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(54) Title: HUMAN PROTEINS HAVING HYDROPHOBIC DOMAINS AND DNAs ENCODING THESE PROTEINS

(57) Abstract: The present invention provides human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs, transformed eukaryotic cells expressing these DNAs and antibodies directed to these proteins.

DESCRIPTION

Human Proteins Having Hydrophobic Domains and DNAs Encoding These Proteins

TECHNICAL FIELD

The present invention relates to human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs, eukaryotic cells expressing these DNAs and antibodies directed to these proteins. The proteins of the present invention can be employed as pharmaceuticals or as antigens for preparing antibodies directed to these proteins. The human cDNAs of the present invention can be utilized as probes for genetic diagnosis and gene sources for gene therapy. Furthermore, the cDNAs can be utilized as gene sources for producing the proteins encoded by these cDNAs in large quantities. Cells into which these genes are introduced to express secretory proteins or membrane proteins in large quantities can be utilized for detection of the corresponding receptors or ligands, screening of novel small molecule pharmaceuticals and the like. The antibodies of the present invention can be utilized for the detection, quantification, purification and the like of the proteins of the present invention.

BACKGROUND ART

Cells secrete many proteins extracellularly. These secretory proteins play important roles in the proliferation control, the differentiation induction, the material transport, the biophylaxis, and the like of the cells. Unlike intracellular proteins, the secretory proteins exert their actions outside the cells. Therefore, they can be administered in the intracorporeal manner such as the injection or the drip, so that they possess hidden potentialities as pharmaceuticals. In fact, a number of human secretory proteins such as interferons, interleukins, erythropoietin, thrombolytic agents and the like are currently employed as pharmaceuticals. In addition, secretory proteins other than those described above are undergoing clinical trials for developing their use as pharmaceuticals. It is believed that the human cells produce many unknown secretory proteins. Availability of these secretory proteins as well as genes encoding them is expected to lead to development of novel pharmaceuticals utilizing them.

On the other hand, membrane proteins play important roles, as signal receptors, ion channels, transporters and the like in the material transport and the signal transduction through the cell membrane. Examples thereof include receptors for various cytokines, ion

channels for the sodium ion, the potassium ion, the chloride ion and the like, transporters for saccharides and amino acids and the like. The genes for many of them have already been cloned. It has been clarified that abnormalities in these membrane proteins are involved in a number of previously cryptogenic diseases. Therefore, discovery of a new membrane protein is expected to lead to elucidation of the causes of many diseases, so that isolation of new genes encoding the membrane proteins has been desired.

Heretofore, due to difficulty in the purification from human cells, many of these secretory proteins and membrane proteins have been isolated by genetic approaches. A general method is the so-called expression cloning method, in which a cDNA library is introduced into eukaryotic cells to express cDNAs, and the cells secreting, or expressing on the surface of membrane, the protein having the activity of interest are then screened. However, only genes for proteins with known functions can be cloned by using this method.

In general, a secretory protein or a membrane protein possesses at least one hydrophobic domain within the protein. After synthesis on ribosomes, such domain works as a secretory signal or remains in the phospholipid membrane to be entrapped in the membrane. Accordingly, if the existence of a highly hydrophobic domain is observed in the amino acid sequence of a protein encoded by a cDNA when the

whole base sequence of the full-length cDNA is determined, it is considered that the cDNA encodes a secretory protein or a membrane protein.

OBJECTS OF INVENTION

The main object of the present invention is to provide novel human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs, transformed eukaryotic cells that are capable of expressing these DNAs and antibodies directed to these proteins. This object as well as other objects and advantages of the present invention will become apparent to those skilled in the art from the following description with reference to the accompanying drawings.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03372.

Fig. 2 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03375.

Fig. 3 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03376.

Fig. 4 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03377.

Fig. 5 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03378.

Fig. 6 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03379.

Fig. 7 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03380.

Fig. 8 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03396.

Fig. 9 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10678.

Fig. 10 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10688.

SUMMARY OF INVENTION

As the result of intensive studies, the present inventors have successfully cloned cDNAs encoding proteins

having hydrophobic domains from the human full-length cDNA bank, thereby completing the present invention. Thus, the present invention provides a human protein having hydrophobic domain(s), namely a protein comprising any one of an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 10. Moreover, the present invention provides a DNA encoding said protein, exemplified by a cDNA comprising any one of a base sequence selected from the group consisting of SEQ ID NOS: 11 to 30, an expression vector that is capable of expressing said DNA by in vitro translation or in eukaryotic cells, a transformed eukaryotic cell that is capable of expressing said DNA and of producing said protein and an antibody directed to said protein.

DETAILED DESCRIPTION OF THE INVENTION

The proteins of the present invention can be obtained, for example, by a method for isolating proteins from human organs, cell lines or the like, a method for preparing peptides by the chemical synthesis based on the amino acid sequence of the present invention, or a method for producing proteins by the recombinant DNA technology using the DNAs encoding the hydrophobic domains of the present invention. Among these, the method for producing proteins by the recombinant DNA technology is preferably employed. For example, the proteins can be expressed in

vitro by preparing an RNA by in vitro transcription from a vector having the cDNA of the present invention, and then carrying out in vitro translation using this RNA as a template. Alternatively, incorporation of the translated region into a suitable expression vector by the method known in the art may lead to expression of a large amount of the encoded protein in prokaryotic cells such as *Escherichia coli, Bacillus subtilis*, etc., and eukaryotic cells such as yeasts, insect cells, mammalian cells, etc.

In the case where the protein of the present invention is produced by expressing the DNA by in vitro translation, the protein of the present invention can be produced in vitro by incorporating the translated region of this cDNA into a vector having an RNA polymerase promoter, and then adding the vector to an in vitro translation system such as a rabbit reticulocyte lysate or a wheat germ extract, which contains an RNA polymerase corresponding to the promoter. The RNA polymerase promoters are exemplified by T7, T3, SP6 and the like. The vectors containing promoters for these RNA polymerases are exemplified by pKA1, pCDM8, pT3/T7 18, pT7/3 19, pBluescript II and the like. Furthermore, the protein of the present invention can be expressed in the secreted form or the form incorporated in the microsome membrane when a canine pancreas microsome or the like is added to the reaction system.

In the case where the protein of the present invention is produced by expressing the DNA in a microorganism such as *Escherichia coli* etc., a recombinant expression vector in which the translated region of the cDNA of the present invention is incorporated into an expression vector having an origin which is capable of replicating in the microorganism, a promoter, a ribosome-binding site, a cDNA-cloning site, a terminator and the like is constructed. After transformation of the host cells with this expression vector, the resulting transformant is grown, whereby the protein encoded by the cDNA can be produced in large quantities in the microorganism. In this case, a protein fragment containing any translated region can be obtained by adding an initiation codon and a termination codon in front of and behind the selected translated region to express the protein. Alternatively, the protein can be expressed as a fusion protein with another protein. Only the portion of the protein encoded by the cDNA can be obtained by cleaving this fusion protein with a suitable protease. The expression vectors for *Escherichia coli* are exemplified by the pUC series, pBluescript II, the pET expression system, the pGEX expression system and the like.

In the case where the protein of the present invention is produced by expressing the DNA in eukaryotic cells, the protein of the present invention can be produced

as a secretory protein, or as a membrane protein on the surface of cell membrane, by incorporating the translated region of the cDNA into an expression vector for eukaryotic cells that has a promoter, a splicing region, a poly(A) addition site and the like, and then introducing the vector into the eukaryotic cells. The expression vectors are exemplified by pKA1, pED6dpc2, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV vectors, pRS, pYES2 and the like. Examples of eukaryotic cells to be used in general include mammalian cultured cells such as monkey kidney COS7 cells, Chinese hamster ovary CHO cells and the like, budding yeasts, fission yeasts, silkworm cells, Xenopus oocytes and the like. Any eukaryotic cells may be used as long as they are capable of expressing the proteins of the present invention. The expression vector can be introduced into the eukaryotic cells by using a method known in the art such as the electroporation method, the calcium phosphate method, the liposome method, the DEAE-dextran method and the like.

After the protein of the present invention is expressed in prokaryotic cells or eukaryotic cells, the protein of interest can be isolated and purified from the culture by a combination of separation procedures known in the art. Examples of the separation procedures include treatment with a denaturing agent such as urea or a detergent, sonication, enzymatic digestion, salting-out or

solvent precipitation, dialysis, centrifugation, ultrafiltration, gel filtration, SDS-PAGE, isoelectric focusing, ion-exchange chromatography, hydrophobic chromatography, affinity chromatography, reverse phase chromatography and the like.

The proteins of the present invention also include peptide fragments (of 5 amino acid residues or more) containing any partial amino acid sequences in the amino acid sequences represented by SEQ ID NOS: 1 to 10. These peptide fragments can be utilized as antigens for preparation of antibodies. Among the proteins of the present invention, those having the signal sequences are secreted in the form of mature proteins after the signal sequences are removed. Therefore, these mature proteins shall come within the scope of the protein of the present invention. The N-terminal amino acid sequences of the mature proteins can be easily determined by using the method for the determination of cleavage site of a signal sequence [JP-A 8-187100]. Furthermore, some membrane proteins undergo the processing on the cell surface to be converted to the secreted forms. Such proteins or peptides in the secreted forms shall also come within the scope of the protein of the present invention. In the case where sugar chain-binding sites are present in the amino acid sequences of the proteins, expression of the proteins in appropriate eukaryotic cells

affords the proteins to which sugar chains are added. Accordingly, such proteins or peptides to which sugar chains are added shall also come within the scope of the protein of the present invention.

The DNAs of the present invention include all the DNAs encoding the above-mentioned proteins. These DNAs can be obtained by using a method for chemical synthesis, a method for cDNA cloning and the like.

The cDNAs of the present invention can be cloned, for example, from cDNA libraries derived from the human cells. The cDNAs are synthesized by using poly(A)$^+$ RNAs extracted from human cells as templates. The human cells may be cells delivered from the human body, for example, by the operation or may be the cultured cells. The cDNAs can be synthesized by using any method such as the Okayama-Berg method [Okayama, H. and Berg, P., Mol. Cell. Biol. 2: 161-170 (1982)], the Gubler-Hoffman method [Gubler, U. and Hoffman, J., Gene 25: 263-269 (1983)] and the like. However, it is desirable to use the capping method [Kato, S. et al., Gene 150: 243-250 (1994)], as exemplified in Examples, in order to obtain a full-length clone in an effective manner. In addition, commercially available human cDNA libraries can be utilized. The cDNAs of the present invention can be cloned from the cDNA libraries by synthesizing an oligonucleotide on the basis of base sequences of any

portion in the cDNA of the present invention and screening the cDNA libraries using this oligonucleotide as a probe for colony or plaque hybridization according to a method known in the art. In addition, the cDNA fragments of the present invention can be prepared from an mRNA isolated from human cells by the RT-PCR method in which oligonucleotides which hybridize with both termini of the cDNA fragment of interest are synthesized, which are then used as the primers.

The cDNAs of the present invention are characterized in that they comprise any one of the base sequences represented by SEQ ID NOS: 11 to 20 or the base sequences represented by SEQ ID NOS: 21 to 30. Table 1 summarizes the clone number (HP number), the cells from which the cDNA clone was obtained, the total number of bases of the cDNA, and the number of the amino acid residues of the encoded protein, for each of the cDNAs.

Table 1

SEQ ID NO	HP number	Cell	Number of bases	Number of amino acid residues
1, 11, 21	HP03372	Thymus	1308	233
2, 12, 22	HP03375	Kidney	1272	273
3, 13, 23	HP03376	HT-1080	2083	282
4, 14, 24	HP03377	HT-1080	1260	238
5, 15, 25	HP03378	Umbilical cord blood	1720	372
6, 16, 26	HP03379	Umbilical cord blood	2237	146
7, 17, 27	HP03380	Umbilical cord blood	1687	302
8, 18, 28	HP03396	Kidney	963	194
9, 19, 29	HP10678	HT-1080	2667	542
10, 20, 30	HP10688	Thymus	1478	276

The same clones as the cDNAs of the present invention can be easily obtained by screening the cDNA libraries constructed from the human cell lines or human tissues utilized in the present invention using an oligonucleotide probe synthesized on the basis of the base sequence of the cDNA provided in any one of SEQ ID NOS: 11 to 30.

In general, the polymorphism due to the individual differences is frequently observed in human genes. Accordingly, any cDNA in which one or plural nucleotides are added, deleted and/or substituted with other nucleotides in SEQ ID NOS: 11 to 30 shall come within the scope of the present invention.

Similarly, any protein in which one or plural

amino acids are added, deleted and/or substituted with other amino acids resulting from the above-mentioned changes shall come within the scope of the present invention, as long as the protein possesses the activity of the protein having any one of the amino acid sequences represented by SEQ ID NOS: 1 to 10.

The cDNAs of the present invention also include cDNA fragments (of 10 bp or more) containing any partial base sequence in the base sequences represented by SEQ ID NOS: 11 to 20 or in the base sequences represented by SEQ ID NOS: 21 to 30. Also, DNA fragments consisting of a sense strand and an anti-sense strand shall come within this scope. These DNA fragments can be utilized as the probes for the genetic diagnosis.

The antibody of the present invention can be obtained from a serum after immunizing an animal using the protein of the present invention as an antigen. A peptide that is chemically synthesized based on the amino acid sequence of the present invention and a protein expressed in eukaryotic or prokaryotic cells can be used as an antigen. Alternatively, an antibody can be prepared by introducing the above-mentioned expression vector for eukaryotic cells into the muscle or the skin of an animal by injection or by using a gene gun and then collecting a serum therefrom (JP-A 7-313187). Animals that can be used include a mouse, a rat,

a rabbit, a goat, a chicken and the like. A monoclonal antibody directed to the protein of the present invention can be produced by fusing B cells collected from the spleen of the immunized animal with myelomas to generate hybridomas.

In addition to the activities and uses described above, the polynucleotides and proteins of the present invention may exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to

map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine

levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines

including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In Current Protocols in Immunology. J.E.e.a.

Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6-Nordan, R. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark,S.C. and Turner, K.J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect

APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically,

infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down

regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign

by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used

include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief

from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the

present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected

tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the

activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J.J. and Brunswick, M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental

Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al.,

Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complementary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-

mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those

described in: Methylcellulose colony forming assays, Freshney, M.G. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the

present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or

sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and

traumatic wounds and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent

Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-β group, may be useful as a fertility inducing therapeutic, based upon the

ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

<u>Chemotactic/Chemokinetic Activity</u>

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other

trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach,

W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke)).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al.,

Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in: Current

Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)),

ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing,

infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or cardiac cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an

antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

Examples

The present invention is specifically illustrated in more detail by the following Examples, but Examples are not intended to restrict the present invention. The basic procedures with regard to the recombinant DNA and the enzymatic reactions were carried out according to the literature ["Molecular Cloning. A Laboratory Manual", Cold Spring Harbor Laboratory, 1989]. Unless otherwise stated, restriction enzymes and various modifying enzymes to be used were those available from Takara Shuzo. The buffer compositions and the reaction conditions for each of the enzyme reactions were as described in the attached instructions. The cDNA synthesis was carried out according to the literature [Kato, S. et al., Gene 150: 243-250 (1994)].

(1) Selection of cDNAs Encoding Proteins Having Hydrophobic Domains

The cDNA library of fibrosarcoma cell line HT-1080 (WO 98/11217) was used as a cDNA library. Additionally, the cDNA libraries constructed from human thymus mRNA (Clontech),

human kidney mRNA (Clontech) and human umbilical cord blood mRNA (Clontech) were also used.

Full-length cDNA clones were selected from the respective libraries and the whole base sequences thereof were determined to construct a homo-protein cDNA bank consisting of the full-length cDNA clones. The hydrophobicity/hydrophilicity profiles were determined for the proteins encoded by the full-length cDNA clones registered in the homo-protein cDNA bank by the Kyte-Doolittle method [Kyte, J. & Doolittle, R. F., J. Mol. Biol. 157: 105-132 (1982)] to examine the presence or absence of a hydrophobic domain. A clone that has a hydrophobic region being assumed as a secretory signal or a transmembrane domain in the amino acid sequence of the encoded protein was selected as a clone candidate.

(2) Protein Synthesis by In Vitro Translation

The plasmid vector bearing the cDNA of the present invention was used for in vitro transcription/translation with a T_NT rabbit reticulocyte lysate kit (Promega). In this case, [^{35}S]methionine was added to label the expression product with a radioisotope. Each of the reactions was carried out according to the protocols attached to the kit. Two micrograms of the plasmid was subjected to the reaction at 30°C for 90 minutes in the reaction solution of a total volume of 25 µl containing 12.5 µl µ of T_NT rabbit

reticulocyte lysate, 0.5 µl of a buffer solution (attached to the kit), 2 µl of an amino acid mixture (without methionine), 2 µl of [^{35}S]methionine (Amersham) (0.37 MBq/µl), 0.5 µl of T7 RNA polymerase, and 20 U of RNasin. The experiment in the presence of a membrane system was carried out by adding 2.5 µl of a canine pancreas microsome fraction (Promega) to the reaction system. To 3 µl of the reaction solution was added 2 µl of the SDS sampling buffer (125 mM Tris-hydrochloride buffer, pH 6.8, 120 mM 2-mercaptoethanol, 2% SDS solution, 0.025% bromophenol blue and 20% glycerol) and the resulting mixture was heated at 95°C for 3 minutes and then subjected to SDS-polyacrylamide gel electrophoresis. The molecular weight of the translation product was determined by carrying out the autoradiography.

(3) Expression in COS7

Escherichia coli cells harboring the expression vector for the protein of the present invention were cultured at 37°C for 2 hours in 2 ml of the 2 x YT culture medium containing 100 µg/ml of ampicillin, the helper phage M13KO7 (50 µ l) was added thereto, and the cells were then cultured at 37°C overnight. Single-stranded phage particles were obtained by polyethylene glycol precipitation from a supernatant separated by centrifugation. The particles were suspended in 100 µl of 1 mM Tris-0.1 mM EDTA, pH 8 (TE).

The cultured cells derived from monkey kidney,

COS7, were cultured at 37°C in the presence of 5% CO_2 in the Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum. 1 x 10^5 COS7 cells were inoculated into a 6-well plate (Nunc, well diameter: 3 cm) and cultured at 37°C for 22 hours in the presence of 5% CO_2. After the medium was removed, the cell surface was washed with a phosphate buffer solution followed by DMEM containing 50 mM Tris-hydrochloride (pH 7.5) (TDMEM). A suspension containing 1 µl of the single-stranded phage suspension, 0.6 ml of the DMEM medium and 3 µl of TRANSFECTAM™ (IBF) was added to the cells and the cells were cultured at 37°C for 3 hours in the presence of 5% CO_2. After the sample solution was removed, the cell surface was washed with TDMEM, 2 ml per well of DMEM containing 10% fetal calf serum was added, and the cells were cultured at 37°C for 2 days in the presence of 5% CO_2. After the medium was exchanged for a medium containing [^{35}S]cysteine or [^{35}S]methionine, the cells were cultured for one hour. After the medium and the cells were separated each other by centrifugation, proteins in the medium fraction and the cell membrane fraction were subjected to SDS-PAGE.

(4) Preparation of Antibodies

A plasmid vector containing the cDNA of the present invention was dissolved in a phosphate buffer solution (PBS: 145 mM NaCl, 2.68 mM KCl, 8.09 mM Na_2HPO_4, 2 mM KH_2PO_4, pH 7.2) to a concentration of 2 µg/µl. 25 µl each

(a total of 50 μl) of the thus-prepared plasmid solution in PBS was injected into the right and left musculi quadriceps femoris of three mice (ICR line) using a 26 guage needle. After similar injections were repeated for one month at intervals of one week, blood was collected. The collected blood was stored at 4°C overnight to coagulate the blood, and then centrifuged at 8,000 x g for five minutes to obtain a supernatant. NaN_3 was added to the supernatant to a concentration of 0.01% and the mixture was then stored at 4°C. The generation of an antibody was confirmed by immunostaining of COS7 cells into which the corresponding vector had been introduced or by Western blotting using a cell lysate or a secreted product.

(5) Clone Examples

<HP03372> (SEQ ID NOS: 1, 11, and 21)

Determination of the whole base sequence of the cDNA insert of clone HP03372 obtained from cDNA library of human thymus revealed the structure consisting of a 75-bp 5′-untranslated region, a 702-bp ORF, and a 531-bp 3′-untranslated region. The ORF encodes a protein consisting of 233 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 1 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product

of 25 kDa that was almost identical with the molecular weight of 26,281 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 30 kDa to which sugar chains are presumably added. In addition, there exist in the amino acid sequence of this protein two sites at which N-glycosylation may occur (Asn-Ile-Ser at position 34 and Asn-Asn-Ser at position 99). Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from tyrosine at position 20.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to human gastric lipase (Accession No. NP_004181). Table 2 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human gastric lipase (LP). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 65.0% in the entire region.

Table 2

```
HP MWQLLAAACWMLLLGSMYGYDKKGNNANPEANMNISQIISYWGYPYEEYDVTTKDGYILG
   ** **.  *.  .  .**.  .*    *  .  ..**..*****.*.*****  ***.*.*.*****.
LP MWLLLTMASLISVLGTTHGLFGKLHPGSPEVTMNISQMITYWGYPNEEYEVVTEDGYILE

HP IYRIPHGRGCPGRTAPKPAVYLQHGLIASASNWICNLPNNSLAFLLADSGYDVWLGNSRG
   .  ***.*.    .*.*...*.*.*****.***.***.*********.***.***********
LP VNRIPYGKKNSGNTGQRPVVFLQHGLLASATNWISNLPNNSLAFILADAGYDVWLGNSRG

HP NTWSRKHLKLSPKSPEYWAFSLDEMAKYDLPATINFIIEKTGQKRLYYVGHSQGTTIAFI
   ***.*..*   **.*  *.****.************.**..*****.*.**********.**
LP NTWARRNLYYSPDSVEFWAFSFDEMAKYDLPATIDFIVKKTGQKQLHYVGHSQGTTIGFI

HP AFSTNPELAKKIKIFFALAPVVTVKYTQSPMKKLTTLSRRVVKVCDFPSFNLK
   ******.***.**.*.*****.*****.*  ..**   .....  *
LP AFSTNPSLAKRIKTFYALAPVATVKYTKSLINKLRFVPQSLFKFIFGDKIFYPHNFFDQF
```

<HP03375> (SEQ ID NOS: 2, 12, and 22)

Determination of the whole base sequence of the cDNA insert of clone HP03375 obtained from cDNA library of human kidney revealed the structure consisting of a 59-bp 5′-untranslated region, a 822-bp ORF, and a 391-bp 3′-untranslated region. The ORF encodes a protein consisting of 273 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 2 depicts the

hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 30 kDa that was almost identical with the molecular weight of 29,598 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 29 kDa. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from alanine at position 23.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to human hypothetical protein (Accession No. AAB47494). Table 3 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human hypothetical protein (HS). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 35.5% in the entire region.

Table 3

HP	MRGSQEVLLMWLLVLAVGGTEHAYRPGRRVCAVRAHGDPV--SESFVQRVYQP

```
   .. **. . *... . * .. **. ..   *.   .**.  *.**.*
HS MGSRAELCTLLGGFSFLLLLIPGEGAKGGSLRESQGVCSKQTLVVPLHYNESYSQPVYKP

HP FLTTCDGHRACSTYRTIYRTAYRRSPGLAPARPRYACCPGWKRTSGLPGACGAAICQPPC
   .** *.*.* ******.**.  .*.   . .... .**.***.    . .* .***. **
HS YLTLCAGRRICSTYRTMYRVM-WREVRREVQQTHAVCCQGWKKRHPGALTC-EAICAKPC

HP RNGGSCVQPGRCRCPAGWRGDTCQSDVDECSARRGGCPQRCVNTAGSYWCQCWEGHSLSA
    *** **.*..* *..** *. *. *****... . *...* *****. * * ..  *..
HS LNGGVCVRPDQCECAPGWGGKHCHVDVDECRTSITLCSHHCFNTAGSFTCGCPHDLVLGV

HP DGTLCVPKGGPPRVAPNPTGVDSAMKEEVQR-LQSRVDLLEEKLQLVLAPLHSLASQALE
   **  *.  .  *.....  .*.   *. .* *.  .. * ..*.  *..  . *.. .
HS DGRTCMEGSPEPPTSASILSVAVREAEKDERALKQEIHELRGRLE-RLEQWAGQAGAWVR

HP HGLP-DPGSLLVHSFQQL----GRIDSLSEQISFLEEQLGSCSCKKDS
     **  *..*  .  ..*   .**.***.*. .***.**.***...*
HS AVLPVPPEELQPEQVAELWGRGDRIESLSDQVLLLEERLGACSCEDNSLGLGVNHR
```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA448958) among ESTs. However, since they are partial sequences, it can not be

judged whether or not they encode the same protein as the protein of the present invention.

<HP03376> (SEQ ID NOS: 3, 13, and 23)

Determination of the whole base sequence of the cDNA insert of clone HP03376 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 187-bp 5'-untranslated region, a 849-bp ORF, and a 1047-bp 3'-untranslated region. The ORF encodes a protein consisting of 282 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain at the C-terminus. Figure 3 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to human glycoprotein gp55 (Accession No. CAA67711). Table 4 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human glycoprotein gp55 (GP). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 94.3% in the entire region.

Table 4

```
HP MSGSSLPGALALSLLLVSGSLLPGPGAAQNEPRIVTSEEVIIRESLLPVTLQCNLTSSSH
   *******************************************.****************
GP MSGSSLPGALALSLLLVSGSLLPGPGAAQNEPRIVTSEEVIIRDSLLPVTLQCNLTSSSH

HP TLMYSYWTRNGVELTATRKNASNMEYRINKPRAEDSGEYHCVYHFVSAPKANATIEVKAA
   ********.***************************************************
GP TLMYSYWTKNGVELTATRKNASNMEYRINKPRAEDSGEYHCVYHFVSAPKANATIEVKAA

HP PDITGHKRSENKNEGQDAMMYCKSVGYPHPEWIWRKKENGVFEEISNSSGRFFITNKENY
   ********************************.*********************.*****
GP PDITGHKRSENKNEGQDAMMYCKSVGYPHPEWMWRKKENGVFEEISNSSGRFFIINKENY

HP TELSIVNLQITEDPGEYECNATNSIGSASVSTVLRVRSHLAPLWPFLGILAEIIILVVII
   ***.********************************************************
GP TELNIVNLQITEDPGEYECNATNSIGSASVSTVLRVRSHLAPLWPFLGILAEIIILVVII

HP VVYEKRKRPDEVPDDDEPAGPMKTNSTNNPKDKNLRQRNTN
   *****************************.***********
GP VVYEKRKRPDEVPDDDEPAGPMKTNSTNNHKDKNLRQRNTN
```

Furthermore, the search of the GenBank using the

base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA206770) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03377> (SEQ ID NOS: 4, 14, and 24)

Determination of the whole base sequence of the cDNA insert of clone HP03377 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 146-bp 5'-untranslated region, a 717-bp ORF, and a 397-bp 3'-untranslated region. The ORF encodes a protein consisting of 238 amino acid residues and there existed three transmembrane domains. Figure 4 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 27 kDa that was almost identical with the molecular weight of 26,120 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to Caenorhabditis elegans hypothetical protein 32 kDa (Accession No. Q09232). Table 5 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and Caenorhabditis elegans

hypothetical protein 32 kDa (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 48.6% in the entire region other than the C-terminal region.

Table 5

```
HP                                 MSLNEHSMQALSWRKLY-LSRAKLKASS
                                   ..*....  .** .   * ****.*****
CE PSTAGGGSRNGVGSKEGSVTSLRMPLKKAGDDVDLGHRGELDLSEKYNYDLSRAQLKASS

HP RTSALLSGFAMVAMVEVQLDADHDYPPGLLIAFSACTTVLVAVHLFALMISTCILPNIEA
   ******.***** .**  *. *.. *  ***.... *..**.***.***.****** .**
CE RTSALLAGFAMVCLVE--LQYDQSTPKPLLIVLGVVTSLLVSVHLLALMMSTCILPYMEA

HP VSNVHNLNSVKESPHERMHRHIELAWAFSTVIGTLLFLAEVVLLCWVKFLPLKKQPGQPR
   .. ..      .*** ... .*.*.* *** ** ****.*.  .. .*** ..
CE TGCTQ------DSPHIKLKFYIDLSWLFSTCIGLLLFLVEIGVIFYVKFTAVGYPTAGYI

HP PTSKPPASGAAANVSTSGITPGQAAAIASTTIMVPFGLIFIVFAVHFYRSLVSHKTDRQF

CE TTAMLVPVGVVFVVFSYLIHKNRVSHSLGRFKHKVDTMKQFLDVEANLQKSTLAPSTIRD
```

HP QELNELAEFARLQDQLDHRGDHPLTPGSHYA

CE I

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. W25208) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03378> (SEQ ID NOS: 5, 15, and 25)

Determination of the whole base sequence of the cDNA insert of clone HP03378 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 281-bp 5'-untranslated region, a 1119-bp ORF, and a 320-bp 3'-untranslated region. The ORF encodes a protein consisting of 372 amino acid residues and there existed seven putative transmembrane domains. Figure 5 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to human P2Y5-like receptor (Accession No. AAB66322). Table 6 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human P2Y5-like receptor (P2). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 33.9% in the entire region.

Table 6

```
HP                     MLANSSSTNSSVLPCPDYRPTHRLHLVVYSLVLAAGLPLN
                        *.*....*....   ...  ..*. .***.*.  **  *
P2 MGDRRFIDFQFQDSNSSLRPRLGNATANNTCIVD-DSFK--YNLNGAVYSVVFILGLITN

HP ALALWVFLRALRVHSVVSVYMCNLAASDLLFTLSLPVRLSYYALHHWPFPDLLCQTTGAI
   ...*.**   ....* .....  ***.*****. .**..  *   .**** * **...*.
P2 SVSLFVFCFRMKMRSETAIFITNLAVSDLLFVCTLPFKIFYNFNRHWPFGDTLCKISGTA

HP FQMNMYGSCIFLMLINVDRYAAIVHPLRLRHLRRPRVARLLCLGVWALILVFAVPAARVH
   *  *.*** .**  *.***. ***.*.* * .* .* . ..* *** *.*  ...*. .
P2 FLTNIYGSMLFLTCISVDRFLAIVYPFRSRTIRTRRNSAIVCAGVWILVLSGGISAS-LF
```

```
HP RPSRCRYRDLEVRLCFESFSDELWKGRLLPLVLLAEALGFLLPLAAVVYSSGRVFWTLAR
   ....    . ..  ***..*.  .**. *  .... *..**..**   * .*. *..** .
P2 STTN---VNNATTTCFEGLSKRVWKTYLSKITIFIEVVGFIIPLILNVSCSSVVLRTLRK

HP PDA--TQSQRRRKTVRLLLANLVIFLLCFVPYNSTLAVYGLLRSKLVAASVPARDRVRGV
   *..    . ...*..... .....*..*******.* .*.*.**. ....    .*   .
P2 PATLSQIGTNKKKVLKMITVHMAVFVVCFVPYNSVLFLYALVRSQAITNCF--LERFAKI

HP LMVMVL-LAGANCVLDPLVYYFSAEGFRNTLRGLGTPHRARTSATNGTRAALAQSERSAV
   .  ..* **. ** .**..***. *.*....
P2 MYPITLCLATLNCCFDPFIYYFTLESFQKSFYINAHIRMESLFKTETPLTTKPSLPAIQE

HP TTDATRPDAASQGLLRPSDSHSLSSFTQCPQDSAL

P2 EVSDQTTNNGGELMLESTF
```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA993247) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03379> (SEQ ID NOS: 6, 16, and 26)

Determination of the whole base sequence of the cDNA insert of clone HP03379 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 24-bp 5'-untranslated region, a 441-bp ORF, and a 1772-bp 3'-untranslated region. The ORF encodes a protein consisting of 146 amino acid residues and there existed nine putative transmembrane domains. Figure 6 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 18 kDa that was somewhat larger than the molecular weight of 16,062 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA663042) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03380> (SEQ ID NOS: 7, 17, and 27)

Determination of the whole base sequence of the cDNA insert of clone HP03380 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 267-bp 5'-untranslated region, a 909-bp ORF, and a 511-

bp 3′-untranslated region. The ORF encodes a protein consisting of 302 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 7 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 36 kDa that was somewhat larger than the molecular weight of 34,178 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to mouse putative sialyltransferase (Accession No. CAA07446). Table 7 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and mouse putative sialyltransferase (MM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 89.4% in the entire region.

Table 7

```
HP MKAPGRLVLIILCSVVFSAVYILLCCWAGLPLCLATCLDHHFPTGSRPTVPGPLHFSGYS
   *******.*..** ..****...***** **********.*.*...*.************
```

MM MKAPGRLLLLTLCILTFSAVCVFLCCWACLPLCLATCLDRHLPAAPRSTVPGPLHFSGYS

HP SVPDGKPLVREPCRSCAVVSSSGQMLGSGLGAEIDSAECVFRMNQAPTVGFEADVGQRST

    ********.** *.******************.**.****.***********.*******

MM SVPDGKPLIRELCHSCAVVSSSGQMLGSGLGAQIDGAECVLRMNQAPTVGFEEDVGQRST

HP LRVVSHTSVPLLLRNYSHYFQKARDTLYMVWGQGRHMDRVLGGRTYRTLLQLTRMYPGLQ

    .**************.******.*******************************

MM LRVISHTSVPLLLRNYSHYFQHARDTLYVVWGQGRHMDRVLGGRTYRTLLQLTRMYPGLQ

HP VYTFTERMMAYCDQIFQDETGKNRRQSGSFLSTGWFTMILALELCEEIVVYGMVSDSYCR

    ***.

MM VYTFTERMMAYCDQIFQDETGKNRRQSGSFLSTGWFTMILALELCEEIVVYGMVSDSYCS

HP EKSHPSVPYHYFEKGRLDECQMYLAHEQAPRSAHRFITEKAVFSRWAKKRPIVFAHPSWR

    ..*************** ***********************************

MM EKSPRSVPYHYFEKGRLDECQMYRLHEQAPRSAHRFITEKAVFSRWAKKRPIVFAHPSWR

HP TE

MM AK

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the

registration of sequences that shared a homology of 90% or more (for example, Accession No. H50479) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03396> (SEQ ID NOS: 8, 18, and 28)

Determination of the whole base sequence of the cDNA insert of clone HP03396 obtained from cDNA library of human kidney revealed the structure consisting of a 245-bp 5′-untranslated region, a 585-bp ORF, and a 133-bp 3′-untranslated region. The ORF encodes a protein consisting of 194 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 8 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 23 kDa that was somewhat larger than the molecular weight of 21,417 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 22 kDa. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from serine at position 20.

The search of the protein data base using the amino acid sequence of the present protein revealed that the

protein was similar to ostrich lysozyme G (Accession No. P00719). Table 8 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and ostrich lysozyme G (SC). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 42.6% in the entire region.

Table 8

```
HP MSALWLLLGLLALMDLSESSNWGCYGNIQSLDTPGASCGIGRRHGLNYCGVRASERLAEI
                         ****.....**.****  ....  ****** **  ..**
SC                     RTGCYGDVNRVDTTGASCKSAKPEKLNYCGVAASRKIAER

HP DMPYLLKYQPMMQTIGQKYCMDPAVIAGVLSRKSPGDKIL----VNMGDRTSMVQ-DPGS
   *.. . .*......*** *.*******..**.*...* *      . *.  ...* *. *
SC DLQSMDRYKALIKKVGQKLCVDPAVIAGIISRESHAGKALRNGWGDNGNGFGLMQVDRRS

HP QAPTS-WISESQVSQTTEVLTTRIKEIQRRFPTWTPDQYLRGGLCAYSGGAG----YVRS
   . *.. * .*... *.**.*...**.**..** ** .* *.**..**..*.*    * *
SC HKPVGEWNGERHLMQGTEILISMIKAIQKKFPRWTKEQQLKGGISAYNAGPGNVRSYERM

HP SQDLSC-DFCNDVLARAKYLKRHGF
```

. . . *. ***. ***. * *. **.

SC DIGTTHDDYANDVVARAQYYKQHGY

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA453324) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10678> (SEQ ID NOS: 9, 19, and 29)

Determination of the whole base sequence of the cDNA insert of clone HP10678 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 228-bp 5'-untranslated region, a 1629-bp ORF, and a 810-bp 3'-untranslated region. The ORF encodes a protein consisting of 542 amino acid residues and there existed seven putative transmembrane domains. Figure 9 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the

protein was similar to human hypothetical protein KIAA0758 (Accession No. BAA34478). Table 9 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human hypothetical protein KIAA0758 (KI). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 37.9% in the entire region.

Table 9

```
HP                                                MKMKSQATMICCLVFFL
                                                                .*
KI ISAPINSLLQMAKALIKSPSQDEMLPTYLKDLSISIDKAEHEISSSPGSLGAIINILDLL

HP STECSHYRSKIHLKSYSEVANHILDTAAISNWAFIPNK--NASSDLLQSVNLFARQLHIH
   **  .. .*..  .   *.* * **.......*  ....  *.**.**.**. *...*.
KI STVPTQVNSEMMTHVLSTV-NVILGKPVLNTWKVLQQQWTNQSSQLLHSVERFSQALQSG

HP NNSENIVNELFIQTKGFHINHNTSEKSLNFSMSMNNTTEDILGMVQIPRQELRKLWPNAS
   ...    .. .*..  *. . .*   ..  ..  .  *. * * * .  * .* ...*
KI DSPPLSFSQTNVQMSSTVIKSSHPE---TYQQRFVFPYFDLWGNVVIDKSYLENL-QSDS
```

HP QAISIAFPTLGAILREAHLQNVSLPRQVNGLVLSVVLPERLQEIILTFEKINKTRNARAQ

...***** *** .. .*   . * . ..*   . ... * .** * *..... ..

KI SIVTMAFPTLQAILAQDIQENNFAESLVMTTTVSHNTTMPFR-ISMTF-KNNSPSGGETK

HP CVGWHSK----KRRWDEKACQMMLDIRNEVKCRCNY--TSVVMSFSILMSSKSMTDKVLD

** *. .   . **...* . . ..*.* *.. . .. .*. . .**

KI CVFWNFRLANNTGGWDSSGCYVEEGDGDNVTCICDHLTSFSILMSPDSPDPSSLLGILLD

HP YITCIGLSVSILSLVLCLIIEATVWSRVVVTEISYMRHVCIVNIAVSLLTANVWFIIGSH

..... *****. **..**.**..*. . .*****.******.***.**.***. .

KI IISYVGVGFSILSLAACLVVEAVVWKSVTKNRTSYMRHTCIVNIAASLLVANTWFIVVA-

HP FNIKAQDYNMC----VAVTFFSHFFYLSLFFWMLFKALLIIYGILVIFRRMMKSRMMVIG

.*... * .*   **.*** ******.***** .*...* .. *..   .* ..*.

KI -AIQDNRYILCKTACVAATFFIHFFYLSVFFWMLTLGLMLFYRLVFILHETSRSTQKAIA

HP FAIGYGCPLIIAVTTVAITEPENGYMRPEACWLNWDNTKALLAFAIPAFVIVAVNLIVVL

* .****** *.*.*.. *.* . * * ..*****..***********..**.**.....

KI FCLGYGCPLAISVITLGATQPREVYTRKNVCWLNWEDTKALLAFAIPALIIVVVNITITI

HP VVAVNTQRPSIGSSK-SQDVVIIMRISKNVAILTPLLGLTWGFGIATLIEGTSLTFHIIF

** ... *****.. .*.   ...***....************..*.. **.*.*****

KI VVITKILRPSIGDKPCKQEKSSLFQISKSIGVLTPLLGLTWGFGLTTVFPGTNLVFHIIF

HP ALLNAFQGFFILLFGTIMDHKIRDALRMRMSSLKGKSRAAENASLGPTNGSKLMNRQG

*.**.***.****** . * *...** ..* . .*. ....***..

KI AILNVFQGLFILLFGCLWDLKVQEALLNKFSLSRWSSQHSKSTSLGSSTPVFSMSSPISR

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA035425) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10688> (SEQ ID NOS: 10, 20, and 30)

Determination of the whole base sequence of the cDNA insert of clone HP10688 obtained from cDNA library of human thymus revealed the structure consisting of a 173-bp 5'-untranslated region, a 831-bp ORF, and a 474-bp 3'-untranslated region. The ORF encodes a protein consisting of 276 amino acid residues and there existed a putative secretory signal at the N-terminus and one transmembrane domain at the C-terminus. Figure 10 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 33 kDa that was somewhat larger than the molecular weight of 29,703 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to human uroplakin III (Accession No. AAC34888). Table 10 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human uroplakin III (UR). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 34.3% in the entire region other than the C-terminal region.

Table 10

```
HP MGLPWGQPHLGLQMLLLALNCLRPSLSLELVPYTPQITAWDLEGKVTATTFSLEQPRCVF
                  ****.*** . ...* *  . .*    ... * ** .**.* *.*
UR          MPPLWALLALGCLRFGSAVNLQPQLASVT--FATNNPTLTTVALEKPLCMF

HP DGLAS--ASDTVWLVVAFSNASRGFQNPETLADIPASPQLL-----TDGHY--MTLPLSP
   *. ..  ....*.* *  ..* .  .. .. ...* .. .*      .*.*  ... * *
UR DSKEALTGTHEVYLYVLVDSAISRNASVQDSTNTPLGSTFLQTEGGRTGPYKAVAFDLIP

HP -DQLPCGDPMAG-SGGAPVL-----RVGHDHGCHQQP----FCNAPLPGPGPYRVKFLLM
    ..**. *.... * ....*     *** . .*  .*    .*****.... ** *..*.
```

```
UR CSDLPSLDAIGDVSKASQILNAYLVRVGANGTCLWDPNFQGLCNAPLSAATEYRFKYVLV

HP D-TRGSPRAETKWSDPITLHQGKTPGSIDTWPGRRSGSMIVITSILSSLAGLLLLAFLAA
   . . *   ..* *****  .* .. ..**********.********.**. .**..* .*
UR NMSTGLVEDQTLWSDPIRTNQLTPYSTIDTWPGRRSGGMIVITSILGSLPFFLLVGFAGA

HP STMRFSSLWWPEEAPEQLRIGSFMGKRYMTHHIPPSEAATLPVGCKPGLDPLPSLSP
    ....  ..
UR IALSLVDMGSSDGETTHDSQITQEAVPKSLGASESSYTSVNRGPPLDRAEVYSSKLQD
```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA464826) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

INDUSTRIAL APPLICABILITY

The present invention provides human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs and eukaryotic cells expressing these DNAs. Since all of the proteins of the present invention are secreted or exist in the cell membrane,

they are considered to be proteins controlling the proliferation and/or the differentiation of the cells. Accordingly, the proteins of the present invention can be employed as pharmaceuticals such as carcinostatic agents which act to control the proliferation and/or the differentiation of the cells, or as antigens for preparing antibodies against these proteins. The DNAs of the present invention can be utilized as probes for the genetic diagnosis and gene sources for the gene therapy. Furthermore, the DNAs can be utilized for expressing these proteins in large quantities. Cells into which these genes are introduced to express these proteins can be utilized for detection of the corresponding receptors or ligands, screening of novel small molecule pharmaceuticals and the like. The antibody of the present invention can be utilized for the detection, quantification, purification and the like of the protein of the present invention.

The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3'

untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, Trends Pharmacol. Sci. 15(7): 250-254; Lavarosky et al., 1997, Biochem. Mol. Med. 62(1): 11-22; and Hampel, 1998, Prog. Nucleic Acid Res. Mol. Biol. 58: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the

transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, Bioessays 14(9): 629-633; Zwaal et al., 1993, Proc. Natl. Acad. Sci. USA 90(16): 7431-7435; Clark et al., 1994, Proc. Natl. Acad. Sci. USA 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour et al., 1988, Nature 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614, 396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the

development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s). Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein

fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide, as determined by those of skill in the art. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Table 11

Stringency Condition	Poly-nucleotide Hybrid	Hybrid Length (bp)[‡]	Hybridization Temperature and Buffer[†]	Wash Temperature and Buffer[†]
A	DNA : DNA	≥50	65°C; 1×SSC -or- 42°C; 1×SSC, 50% formamide	65°C; 0.3×SSC
B	DNA : DNA	<50	T_B*; 1×SSC	T_B*; 1×SSC
C	DNA : RNA	≥50	67°C; 1×SSC -or- 45°C; 1×SSC, 50% formamide	67°C; 0.3×SSC
D	DNA : RNA	<50	T_D*; 1×SSC	T_D*; 1×SSC
E	RNA : RNA	≥50	70°C; 1×SSC -or- 50°C; 1×SSC, 50% formamide	70°C; 0.3×SSC
F	RNA : RNA	<50	T_F*; 1×SSC	T_F*; 1×SSC
G	DNA : DNA	≥50	65°C; 4×SSC -or- 42°C; 4×SSC, 50% formamide	65°C; 1×SSC
H	DNA : DNA	<50	T_H*; 4×SSC	T_H*; 4×SSC
I	DNA : RNA	≥50	67°C; 4×SSC -or- 45°C; 4×SSC, 50% formamide	67°C; 1×SSC
J	DNA : RNA	<50	T_J*; 4×SSC	T_J*; 4×SSC
K	RNA : RNA	≥50	70°C; 4×SSC -or- 50°C; 4×SSC, 50% formamide	67°C; 1×SSC
L	RNA : RNA	<50	T_L*; 2×SSC	T_L*; 2×SSC
M	DNA : DNA	≥50	50°C; 4×SSC -or- 40°C; 6×SSC, 50% formamide	50°C; 2×SSC
N	DNA : DNA	<50	T_N*; 6×SSC	T_N*; 6×SSC
O	DNA : RNA	≥50	55°C; 4×SSC -or- 42°C; 6×SSC, 50% formamide	55°C; 2×SSC
P	DNA : RNA	<50	T_P*; 6×SSC	T_P*; 6×SSC
Q	RNA : RNA	≥50	60°C; 4×SSC -or- 45°C; 6×SSC, 50% formamide	60°C; 2×SSC
R	RNA : RNA	<50	T_R*; 4×SSC	T_R*; 4×SSC

‡ : The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

† : SSPE (1×SSPE is 0.15M NaCl, 10mM NaH_2PO_4, and 1.25mM EDTA, pH7.4) can be substituted for SSC (1×SSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R : The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C)=2(#of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C)=81.5 + 16.6($\log_{10}$[Na^+]) + 0.41 (%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na^+] is the concentration of sodium ions in the hybridization buffer ([Na^+] for 1×SSC=0.165M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and Current Protocols in Molecular Biology, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

CLAIMS

1. A protein comprising any one of an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 10.

2. An isolated DNA encoding the protein according to Claim 1.

3. An isolated cDNA comprising any one of a base sequence selected from the group consisting of SEQ ID NOS: 11 to 20.

4. The cDNA according to Claim 3 consisting of any one of a base sequence selected from the group consisting of SEQ ID NOS: 21 to 30.

5. An expression vector that is capable of expressing the DNA according to any one of Claim 2 to Claim 4 by in vitro translation or in eukaryotic cells.

6. A transformed eukaryotic cell that is capable of expressing the DNA according to any one of Claim 2 to Claim 4 and of producing the protein according to Claim 1.

7. An antibody directed to the protein according to Claim 1.

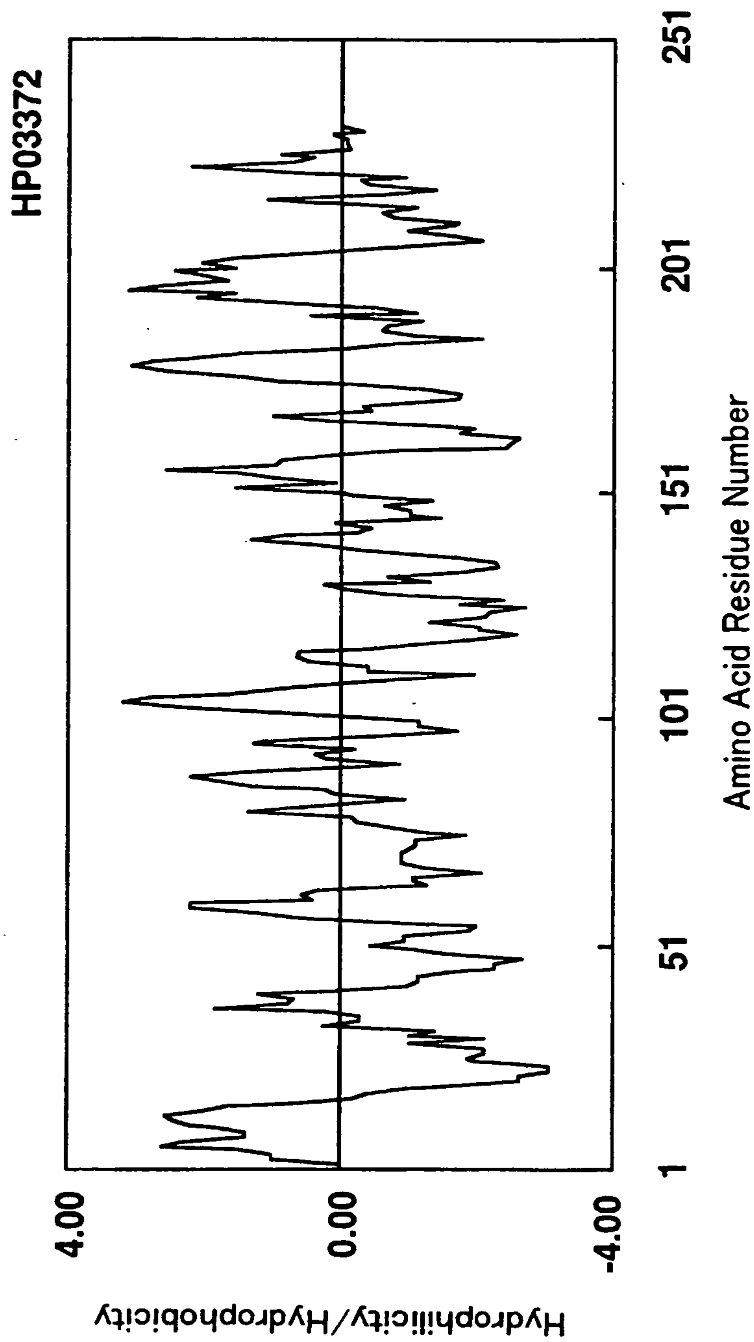
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Fig.1

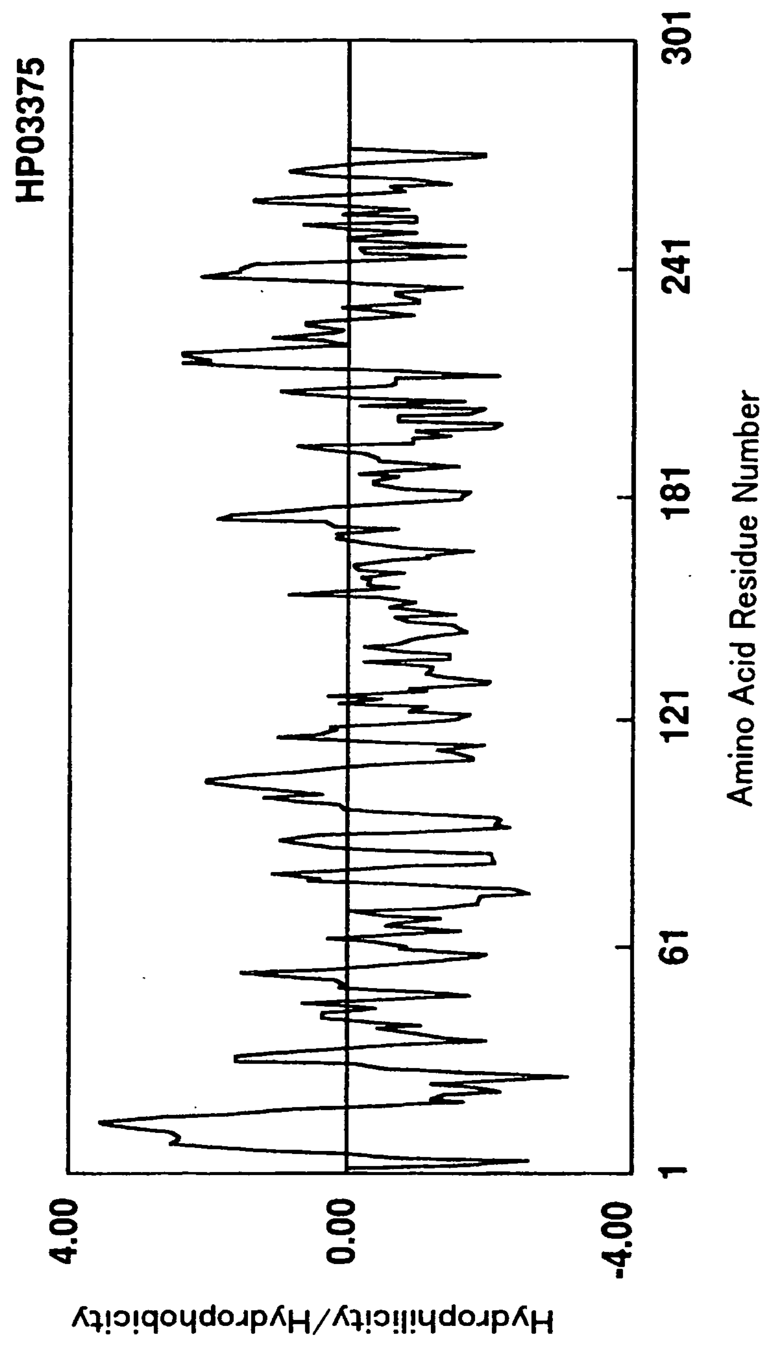
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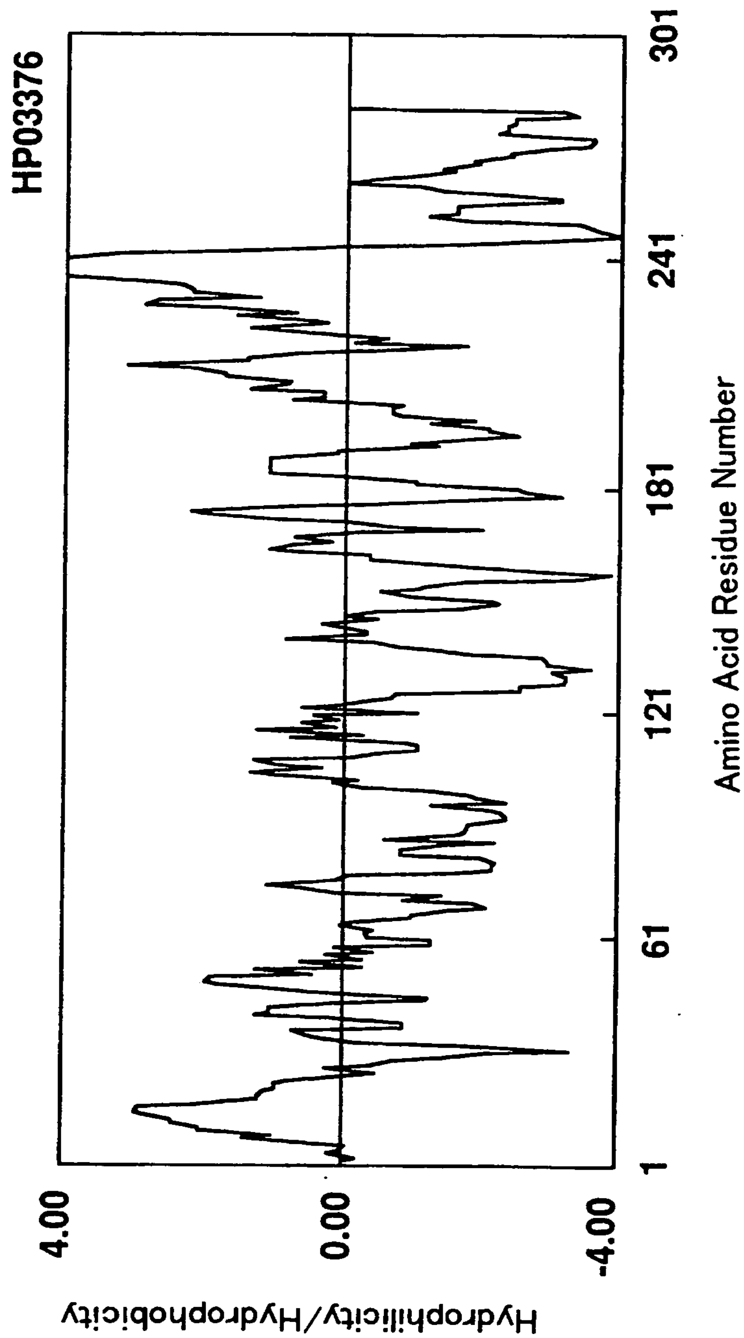
Fig.2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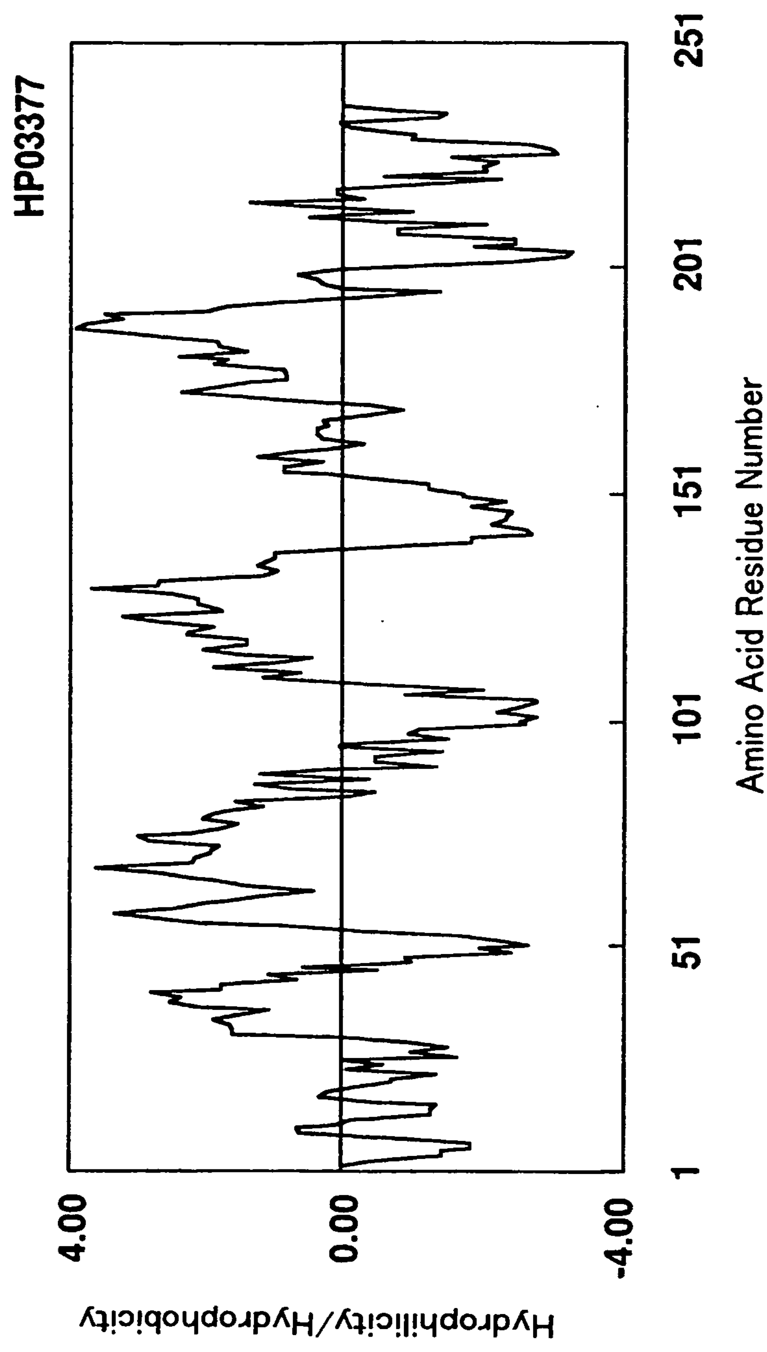
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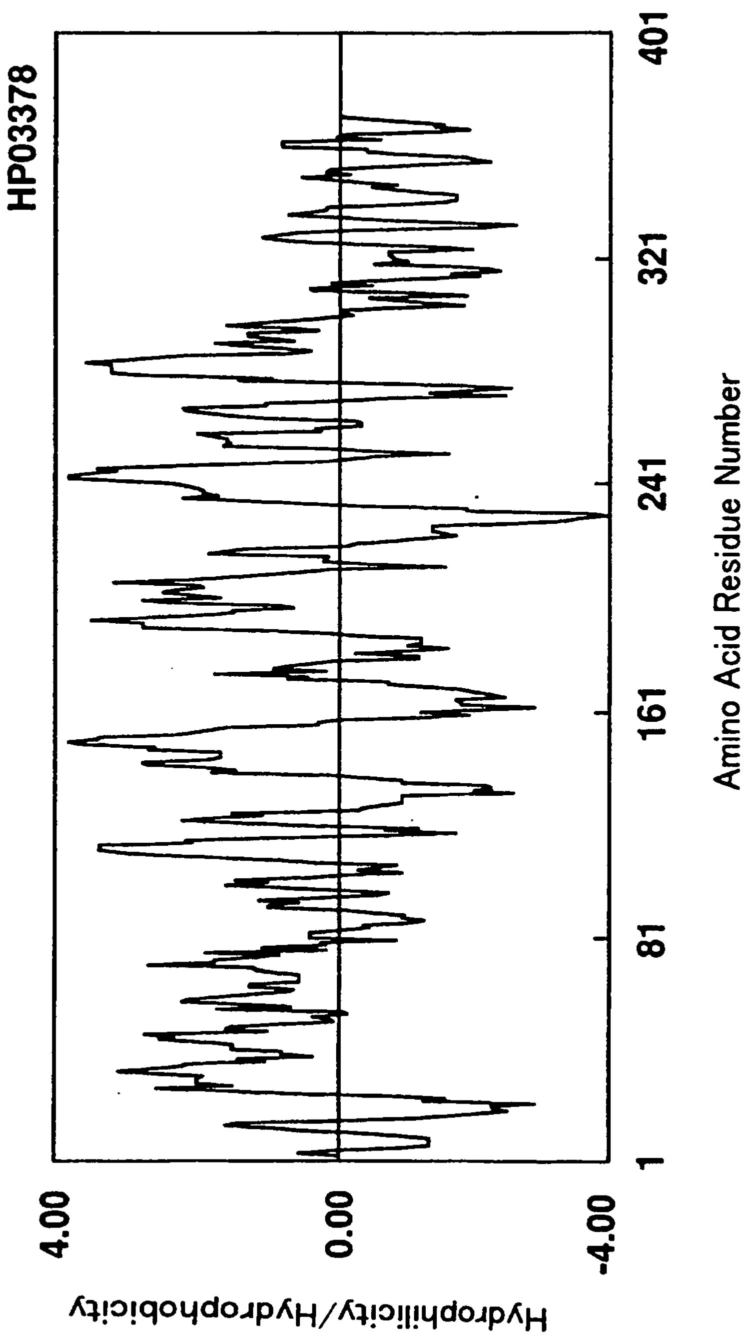
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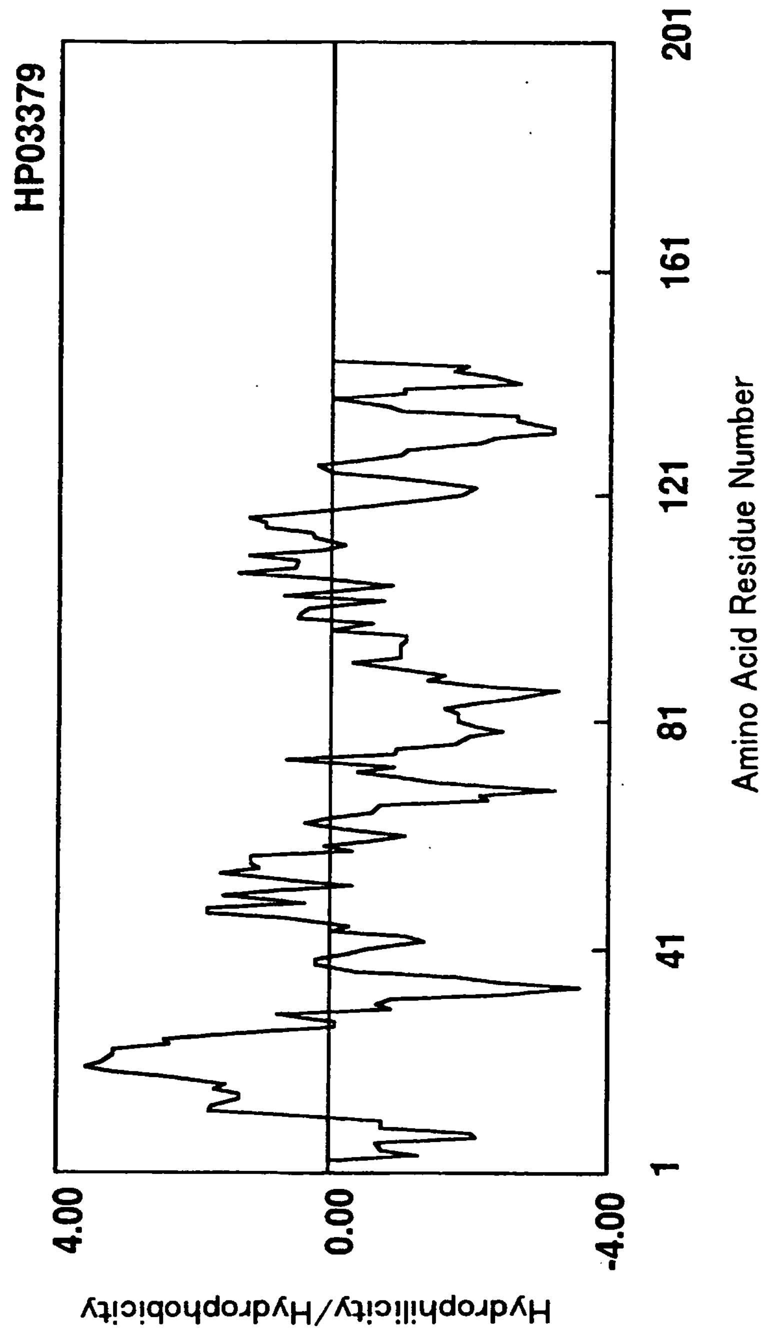
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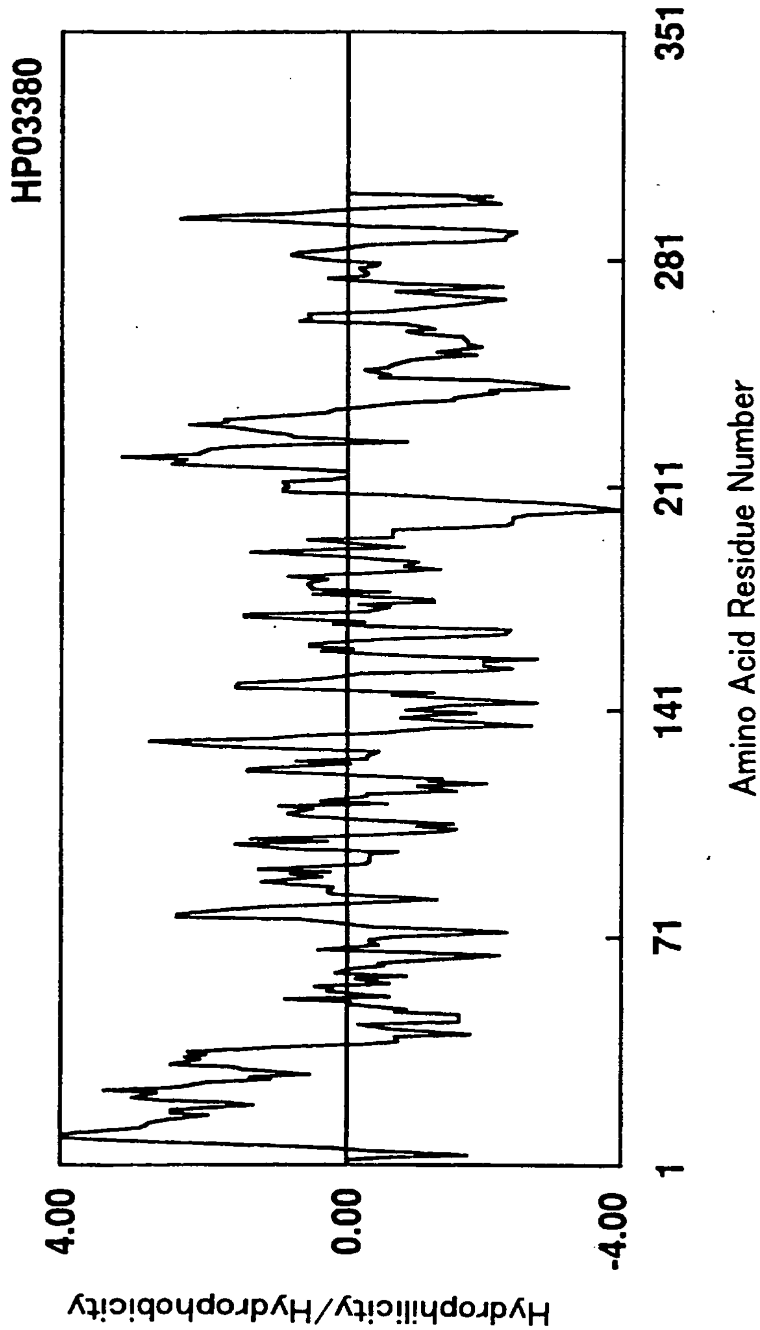
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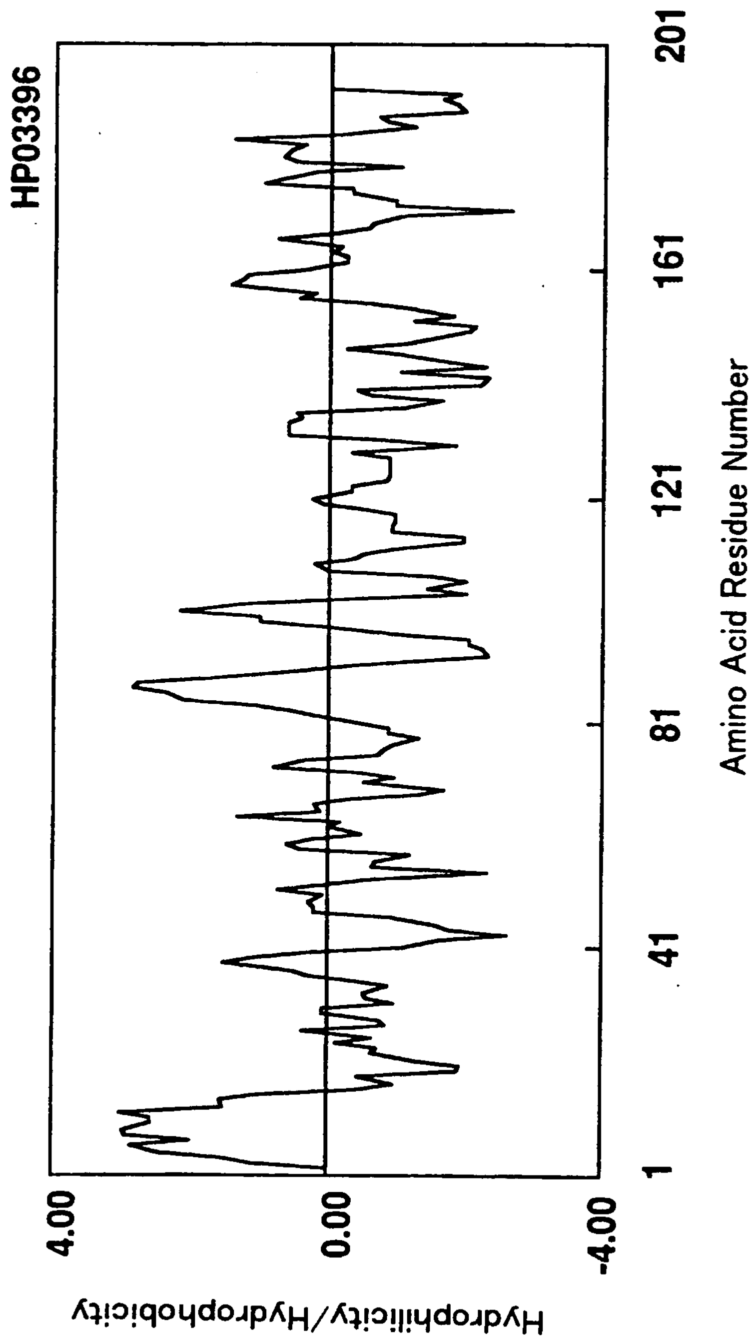
Fig.7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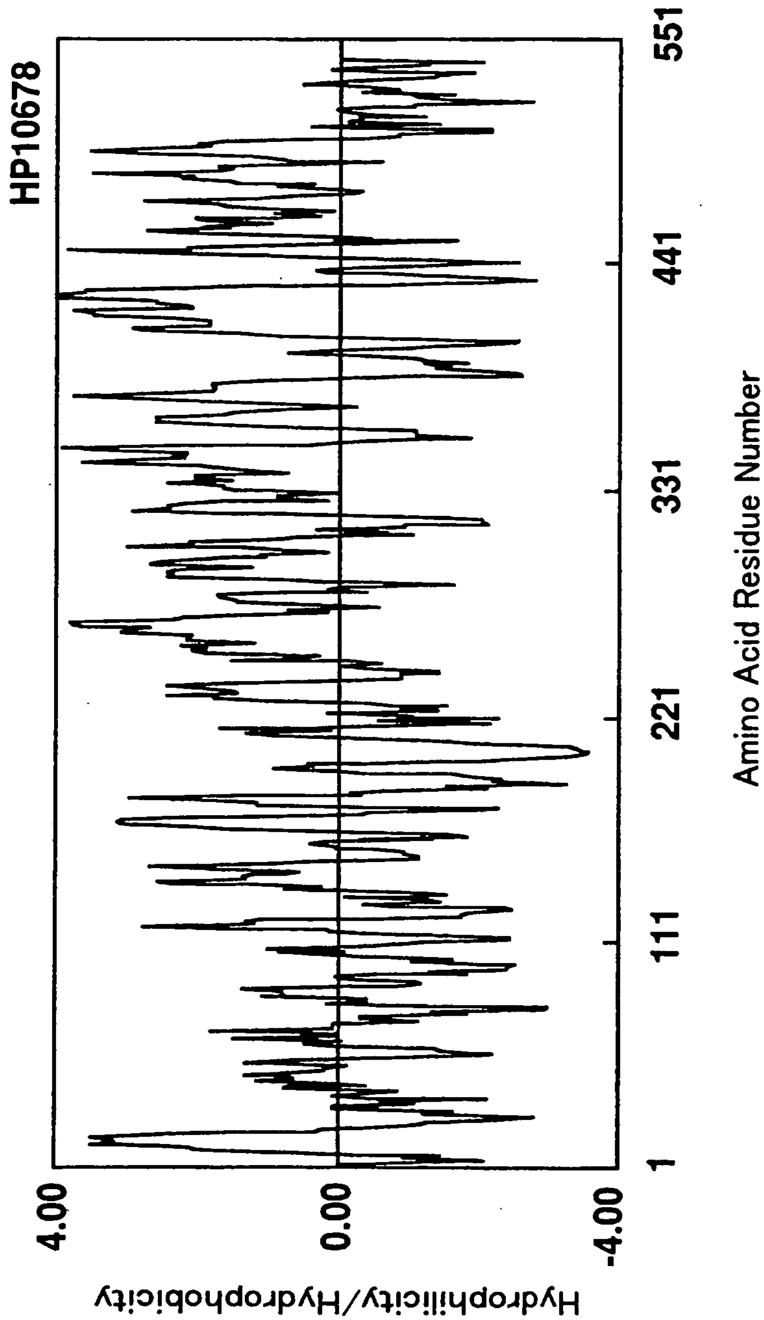
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Fig.9

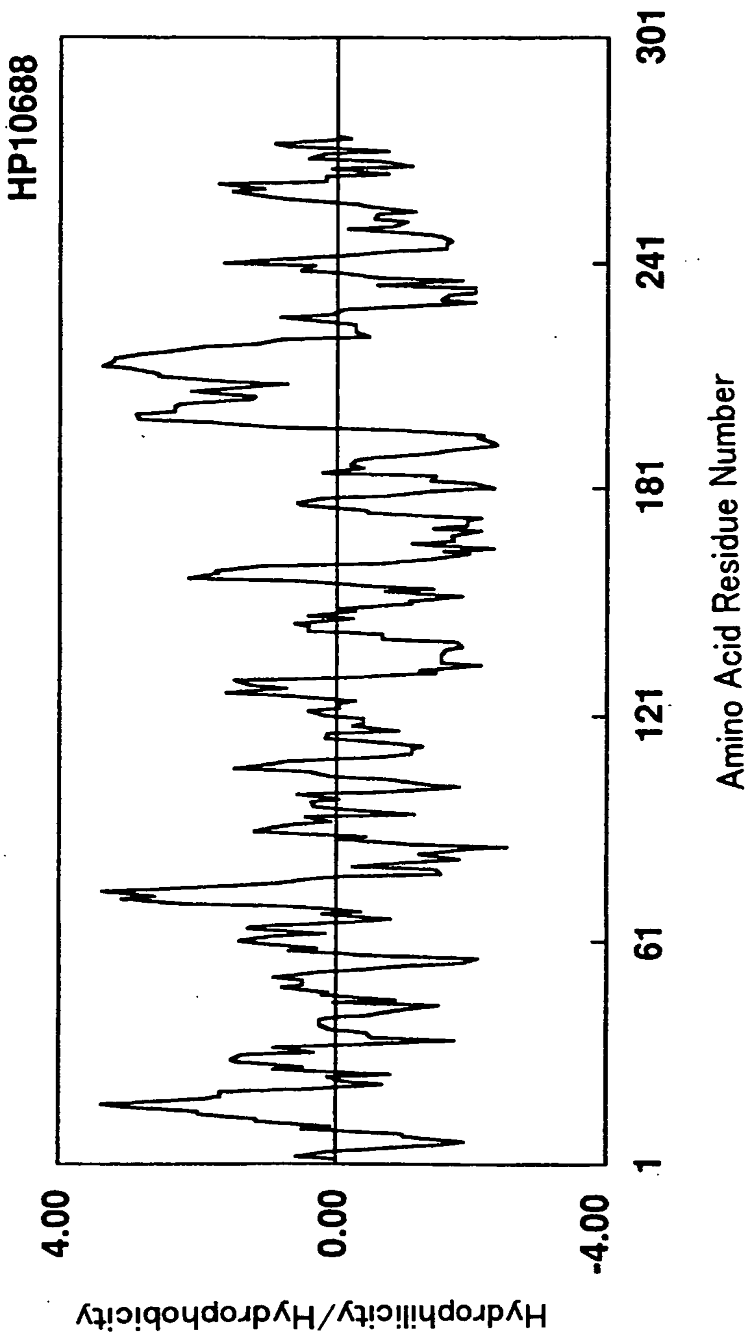
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Fig.10

SEQUENCE LISTING

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Protegene Inc.

<120> Human proteins having hydrophobic domains and DNAs encoding these proteins

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<150> JP 11-188835

<151> 1999-07-02

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Pro His Gly Arg Gly Cys Pro Gly Arg Thr Ala Pro Lys Pro Ala Val
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65 70 75 80

Pro Ala Arg Pro Arg Tyr Ala Cys Cys Pro Gly Trp Lys Arg Thr Ser

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Gly Leu Pro Gly Ala Cys Gly Ala Ala Ile Cys Gln Pro Pro Cys Arg

100 105 110

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Cys Gln Cys Trp Glu Gly His Ser Leu Ser Ala Asp Gly Thr Leu Cys

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Val Pro Lys Gly Gly Pro Pro Arg Val Ala Pro Asn Pro Thr Gly Val

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Trp Pro Phe Leu Gly Ile Leu Ala Glu Ile Ile Ile Leu Val Val Ile

225 230 235 240

Ile Val Val Tyr Glu Lys Arg Lys Arg Pro Asp Glu Val Pro Asp Asp

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65 70 75 80

Ile Leu Pro Asn Ile Glu Ala Val Ser Asn Val His Asn Leu Asn Ser

85 90 95

Val Lys Glu Ser Pro His Glu Arg Met His Arg His Ile Glu Leu Ala

100 105 110

Trp Ala Phe Ser Thr Val Ile Gly Thr Leu Leu Phe Leu Ala Glu Val

115 120 125

Val Leu Leu Cys Trp Val Lys Phe Leu Pro Leu Lys Lys Gln Pro Gly

130 135 140

Gln Pro Arg Pro Thr Ser Lys Pro Pro Ala Ser Gly Ala Ala Ala Asn

145 150 155 160

Val Ser Thr Ser Gly Ile Thr Pro Gly Gln Ala Ala Ala Ile Ala Ser

165 170 175

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180 185 190

His Phe Tyr Arg Ser Leu Val Ser His Lys Thr Asp Arg Gln Phe Gln

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195 200 205

Tyr Ser Ser Gly Arg Val Phe Trp Thr Leu Ala Arg Pro Asp Ala Thr

210 215 220

Gln Ser Gln Arg Arg Arg Lys Thr Val Arg Leu Leu Leu Ala Asn Leu

225 230 235 240

Val Ile Phe Leu Leu Cys Phe Val Pro Tyr Asn Ser Thr Leu Ala Val

245 250 255

Tyr Gly Leu Leu Arg Ser Lys Leu Val Ala Ala Ser Val Pro Ala Arg

260 265 270

Asp Arg Val Arg Gly Val Leu Met Val Met Val Leu Leu Ala Gly Ala

275 280 285

Asn Cys Val Leu Asp Pro Leu Val Tyr Tyr Phe Ser Ala Glu Gly Phe

290 295 300

Arg Asn Thr Leu Arg Gly Leu Gly Thr Pro His Arg Ala Arg Thr Ser

305 310 315 320

Ala Thr Asn Gly Thr Arg Ala Ala Leu Ala Gln Ser Glu Arg Ser Ala

325 330 335

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Gly Lys Pro Leu Val Arg Glu Pro Cys Arg Ser Cys Ala Val Val Ser

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Ser Ser Gly Gln Met Leu Gly Ser Gly Leu Gly Ala Glu Ile Asp Ser

85 90 95

Ala Glu Cys Val Phe Arg Met Asn Gln Ala Pro Thr Val Gly Phe Glu

100 105 110

Ala Asp Val Gly Gln Arg Ser Thr Leu Arg Val Val Ser His Thr Ser

115 120 125

Val Pro Leu Leu Leu Arg Asn Tyr Ser His Tyr Phe Gln Lys Ala Arg

130 135 140

Asp Thr Leu Tyr Met Val Trp Gly Gln Gly Arg His Met Asp Arg Val

145 150 155 160

Leu Gly Gly Arg Thr Tyr Arg Thr Leu Leu Gln Leu Thr Arg Met Tyr

165 170 175

Pro Gly Leu Gln Val Tyr Thr Phe Thr Glu Arg Met Met Ala Tyr Cys

180 185 190

Asp Gln Ile Phe Gln Asp Glu Thr Gly Lys Asn Arg Arg Gln Ser Gly

195 200 205

Ser Phe Leu Ser Thr Gly Trp Phe Thr Met Ile Leu Ala Leu Glu Leu

210 215 220

Cys Glu Glu Ile Val Val Tyr Gly Met Val Ser Asp Ser Tyr Cys Arg

225 230 235 240

Glu Lys Ser His Pro Ser Val Pro Tyr His Tyr Phe Glu Lys Gly Arg

245 250 255

Leu Asp Glu Cys Gln Met Tyr Leu Ala His Glu Gln Ala Pro Arg Ser

260 265 270

Ala His Arg Phe Ile Thr Glu Lys Ala Val Phe Ser Arg Trp Ala Lys

275 280 285

Lys Arg Pro Ile Val Phe Ala His Pro Ser Trp Arg Thr Glu

290 295 300

<210> 8

<211> 194

<212> PRT

<213> Homo sapiens

<400> 8

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Thr Pro Gly Ala Ser Cys Gly Ile Gly Arg Arg His Gly Leu Asn Tyr
35 40 45

Cys Gly Val Arg Ala Ser Glu Arg Leu Ala Glu Ile Asp Met Pro Tyr
50 55 60

Leu Leu Lys Tyr Gln Pro Met Met Gln Thr Ile Gly Gln Lys Tyr Cys
65 70 75 80

Met Asp Pro Ala Val Ile Ala Gly Val Leu Ser Arg Lys Ser Pro Gly
85 90 95

Asp Lys Ile Leu Val Asn Met Gly Asp Arg Thr Ser Met Val Gln Asp
100 105 110

Pro Gly Ser Gln Ala Pro Thr Ser Trp Ile Ser Glu Ser Gln Val Ser
115 120 125

Gln Thr Thr Glu Val Leu Thr Thr Arg Ile Lys Glu Ile Gln Arg Arg
130 135 140

Phe Pro Thr Trp Thr Pro Asp Gln Tyr Leu Arg Gly Gly Leu Cys Ala
145 150 155 160
Tyr Ser Gly Gly Ala Gly Tyr Val Arg Ser Ser Gln Asp Leu Ser Cys
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Asp Phe Cys Asn Asp Val Leu Ala Arg Ala Lys Tyr Leu Lys Arg His
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Gly Phe

<210> 9
<211> 542
<212> PRT
<213> Homo sapiens

<400> 9
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35 40 45
Trp Ala Phe Ile Pro Asn Lys Asn Ala Ser Ser Asp Leu Leu Gln Ser
50 55 60
Val Asn Leu Phe Ala Arg Gln Leu His Ile His Asn Asn Ser Glu Asn
65 70 75 80

Ile Val Asn Glu Leu Phe Ile Gln Thr Lys Gly Phe His Ile Asn His
85 90 95
Asn Thr Ser Glu Lys Ser Leu Asn Phe Ser Met Ser Met Asn Asn Thr
100 105 110
Thr Glu Asp Ile Leu Gly Met Val Gln Ile Pro Arg Gln Glu Leu Arg
115 120 125
Lys Leu Trp Pro Asn Ala Ser Gln Ala Ile Ser Ile Ala Phe Pro Thr
130 135 140
Leu Gly Ala Ile Leu Arg Glu Ala His Leu Gln Asn Val Ser Leu Pro
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Arg Gln Val Asn Gly Leu Val Leu Ser Val Val Leu Pro Glu Arg Leu
165 170 175
Gln Glu Ile Ile Leu Thr Phe Glu Lys Ile Asn Lys Thr Arg Asn Ala
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Arg Ala Gln Cys Val Gly Trp His Ser Lys Lys Arg Arg Trp Asp Glu
195 200 205
Lys Ala Cys Gln Met Met Leu Asp Ile Arg Asn Glu Val Lys Cys Arg
210 215 220
Cys Asn Tyr Thr Ser Val Val Met Ser Phe Ser Ile Leu Met Ser Ser
225 230 235 240
Lys Ser Met Thr Asp Lys Val Leu Asp Tyr Ile Thr Cys Ile Gly Leu
245 250 255
Ser Val Ser Ile Leu Ser Leu Val Leu Cys Leu Ile Ile Glu Ala Thr
260 265 270
Val Trp Ser Arg Val Val Val Thr Glu Ile Ser Tyr Met Arg His Val

275 280 285

Cys Ile Val Asn Ile Ala Val Ser Leu Leu Thr Ala Asn Val Trp Phe

290 295 300

Ile Ile Gly Ser His Phe Asn Ile Lys Ala Gln Asp Tyr Asn Met Cys

305 310 315 320

Val Ala Val Thr Phe Phe Ser His Phe Phe Tyr Leu Ser Leu Phe Phe

325 330 335

Trp Met Leu Phe Lys Ala Leu Leu Ile Ile Tyr Gly Ile Leu Val Ile

340 345 350

Phe Arg Arg Met Met Lys Ser Arg Met Met Val Ile Gly Phe Ala Ile

355 360 365

Gly Tyr Gly Cys Pro Leu Ile Ile Ala Val Thr Thr Val Ala Ile Thr

370 375 380

Glu Pro Glu Asn Gly Tyr Met Arg Pro Glu Ala Cys Trp Leu Asn Trp

385 390 395 400

Asp Asn Thr Lys Ala Leu Leu Ala Phe Ala Ile Pro Ala Phe Val Ile

405 410 415

Val Ala Val Asn Leu Ile Val Val Leu Val Val Ala Val Asn Thr Gln

420 425 430

Arg Pro Ser Ile Gly Ser Ser Lys Ser Gln Asp Val Val Ile Ile Met

435 440 445

Arg Ile Ser Lys Asn Val Ala Ile Leu Thr Pro Leu Leu Gly Leu Thr

450 455 460

Trp Gly Phe Gly Ile Ala Thr Leu Ile Glu Gly Thr Ser Leu Thr Phe

465 470 475 480

His Ile Ile Phe Ala Leu Leu Asn Ala Phe Gln Gly Phe Phe Ile Leu

485 490 495

Leu Phe Gly Thr Ile Met Asp His Lys Ile Arg Asp Ala Leu Arg Met

500 505 510

Arg Met Ser Ser Leu Lys Gly Lys Ser Arg Ala Ala Glu Asn Ala Ser

515 520 525

Leu Gly Pro Thr Asn Gly Ser Lys Leu Met Asn Arg Gln Gly

530 535 540

<210> 10

<211> 276

<212> PRT

<213> Homo sapiens

<400> 10

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Tyr Thr Pro Gln Ile Thr Ala Trp Asp Leu Glu Gly Lys Val Thr Ala

35 40 45

Thr Thr Phe Ser Leu Glu Gln Pro Arg Cys Val Phe Asp Gly Leu Ala

50 55 60

Ser Ala Ser Asp Thr Val Trp Leu Val Val Ala Phe Ser Asn Ala Ser

65 70 75 80

Arg Gly Phe Gln Asn Pro Glu Thr Leu Ala Asp Ile Pro Ala Ser Pro

85 90 95

Gln Leu Leu Thr Asp Gly His Tyr Met Thr Leu Pro Leu Ser Pro Asp

100 105 110

Gln Leu Pro Cys Gly Asp Pro Met Ala Gly Ser Gly Gly Ala Pro Val

115 120 125

Leu Arg Val Gly His Asp His Gly Cys His Gln Gln Pro Phe Cys Asn

130 135 140

Ala Pro Leu Pro Gly Pro Gly Pro Tyr Arg Val Lys Phe Leu Leu Met

145 150 155 160

Asp Thr Arg Gly Ser Pro Arg Ala Glu Thr Lys Trp Ser Asp Pro Ile

165 170 175

Thr Leu His Gln Gly Lys Thr Pro Gly Ser Ile Asp Thr Trp Pro Gly

180 185 190

Arg Arg Ser Gly Ser Met Ile Val Ile Thr Ser Ile Leu Ser Ser Leu

195 200 205

Ala Gly Leu Leu Leu Leu Ala Phe Leu Ala Ala Ser Thr Met Arg Phe

210 215 220

Ser Ser Leu Trp Trp Pro Glu Glu Ala Pro Glu Gln Leu Arg Ile Gly

225 230 235 240

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Ala Ala Thr Leu Pro Val Gly Cys Lys Pro Gly Leu Asp Pro Leu Pro

260 265 270

Ser Leu Ser Pro

275

<210> 11

<211> 699

<212> DNA

<213> Homo sapiens

<400> 11

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tactggggtt atccttatga agagtatgat gttacaacaa aagatggtta tatccttgga 180

atttatagga ttccacatgg aagaggatgc ccagggagga cagctccaaa gcctgctgtg 240

tatttgcagc atggcttaat tgcatctgcc agtaactgga tttgcaacct gcccaacaac 300

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agtttggatg agatggctaa atatgacctt ccagccacaa tcaattttat catagagaaa 480

actggacaga agcgactcta ctacgtgggc cactcacaag gcaccaccat agcttttata 540

gcattttcta caaacccaga actggctaaa aagattaaga tatttttgc actggctcca 600

gttgtcacag ttaaatacac ccaaagtcct atgaaaaaac taacaaccct ttccaggcga 660

gtagttaagg tatgtgactt cccaagtttt aatctgaaa 699

<210> 12

<211> 819

<212> DNA

<213> Homo sapiens

<400> 12

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tccgagtcgt tcgtgcagcg tgtgtaccag cccttcctca ccacctgcga cgggcaccgg 180

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gcctgtggag cagcaatatg ccagccgcca tgccggaacg gagggagctg tgtccagcct 360

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<210> 13

<211> 846

<212> DNA

<213> Homo sapiens

<400> 13

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<210> 14

<211> 714

<212> DNA

<213> Homo sapiens

<400> 14

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atggtggagg tgcagctgga cgctgaccac gactacccac cggggctgct catcgccttc    180
agtgcctgca ccacagtgct ggtggctgtg cacctgtttg cgctcatgat cagcacctgc    240
atcctgccca acatcgaggc ggtgagcaac gtgcacaatc tcaactcggt caaggagtcc    300
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acgctgctct tcctagctga ggtggtgctg ctctgctggg tcaagttctt gcccctcaag 420

aagcagccag gccagccaag gcccaccagc aagcccccg ccagtggcgc agcagccaac 480

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cataagaccg accgacagtt ccaggagctc aacgagctgg cggagtttgc ccgcttacag 660

gaccagctgg accacagagg ggaccacccc ctgacgcccg gcagccacta tgcc 714

<210> 15

<211> 1116

<212> DNA

<213> Homo sapiens

<400> 15

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<210> 16

<211> 438

<212> DNA

<213> Homo sapiens

<400> 16

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ccggggccgc cggggctgcc atttatcggc aacatctatt ccctggcagc ctcatccgag 180

cttccccatg tctacatgag aaagcagagc caggtgtacg gagaggtaca gccccgacgg 240

gccccgggca gggagggccg ccaggctggc ccgggctggc cagggccttc ctggttggac 300

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gagccccgcc cctgccgg 438

<210> 17

<211> 906

<212> DNA

<213> Homo sapiens

<400> 17

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<210> 18

<211> 582

<212> DNA

<213> Homo sapiens

<400> 18

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<210> 19

<211> 1626

<212> DNA

<213> Homo sapiens

<400> 19

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<211> 828

<212> DNA

<213> Homo sapiens

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<211> 1308

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (76)...(777)

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Met Trp Gln Leu Leu Ala Ala Ala Cys Trp Met Leu

1 5 10

ctt ctt gga tct atg tat ggt tat gac aag aaa gga aac aat gca aac 159

Leu Leu Gly Ser Met Tyr Gly Tyr Asp Lys Lys Gly Asn Asn Ala Asn

15 20 25

cct gaa gct aat atg aat att agc cag att att tct tac tgg ggt tat 207

Pro Glu Ala Asn Met Asn Ile Ser Gln Ile Ile Ser Tyr Trp Gly Tyr

30 35 40

cct tat gaa gag tat gat gtt aca aca aaa gat ggt tat atc ctt gga 255

Pro Tyr Glu Glu Tyr Asp Val Thr Thr Lys Asp Gly Tyr Ile Leu Gly

45 50 55 60

att tat agg att cca cat gga aga gga tgc cca ggg agg aca gct cca 303

Ile Tyr Arg Ile Pro His Gly Arg Gly Cys Pro Gly Arg Thr Ala Pro

65 70 75

aag cct gct gtg tat ttg cag cat ggc tta att gca tct gcc agt aac 351

Lys Pro Ala Val Tyr Leu Gln His Gly Leu Ile Ala Ser Ala Ser Asn

80 85 90

tgg att tgc aac ctg ccc aac aac agt ttg gct ttc ctt ctg gca gat 399

Trp Ile Cys Asn Leu Pro Asn Asn Ser Leu Ala Phe Leu Leu Ala Asp
95 100 105
agt ggt tat gac gtg tgg ttg ggg aac agc cga gga aac act tgg tcc 447
Ser Gly Tyr Asp Val Trp Leu Gly Asn Ser Arg Gly Asn Thr Trp Ser
110 115 120
aga aaa cac ctt aaa ttg tca ccg aaa tca cca gaa tac tgg gcc ttc 495
Arg Lys His Leu Lys Leu Ser Pro Lys Ser Pro Glu Tyr Trp Ala Phe
125 130 135 140
agt ttg gat gag atg gct aaa tat gac ctt cca gcc aca atc aat ttt 543
Ser Leu Asp Glu Met Ala Lys Tyr Asp Leu Pro Ala Thr Ile Asn Phe
145 150 155
atc ata gag aaa act gga cag aag cga ctc tac tac gtg ggc cac tca 591
Ile Ile Glu Lys Thr Gly Gln Lys Arg Leu Tyr Tyr Val Gly His Ser
160 165 170
caa ggc acc acc ata gct ttt ata gca ttt tct aca aac cca gaa ctg 639
Gln Gly Thr Thr Ile Ala Phe Ile Ala Phe Ser Thr Asn Pro Glu Leu
175 180 185
gct aaa aag att aag ata ttt ttt gca ctg gct cca gtt gtc aca gtt 687
Ala Lys Lys Ile Lys Ile Phe Phe Ala Leu Ala Pro Val Val Thr Val
190 195 200
aaa tac acc caa agt cct atg aaa aaa cta aca acc ctt tcc agg cga 735
Lys Tyr Thr Gln Ser Pro Met Lys Lys Leu Thr Thr Leu Ser Arg Arg
205 210 215 220
gta gtt aag gta tgt gac ttc cca agt ttt aat ctg aaa taacta 780
Val Val Lys Val Cys Asp Phe Pro Ser Phe Asn Leu Lys

225 230

aaagtagctc tatttccatt gatttcaaca gaagaccaat gacattttac aaacttctga 840

gaaaataata ggtattcaag atatccatgt aagttcactg atgatgtatg caatcttatt 900

agcagagttc agggaactcc ccctgttgct aatctgccct actttcttca tctatgtcta 960

gaaacgtgtc tgctgcgcca ttcctcaacc acagatagag agaacttatt tgattgattg 1020

gtttgttgaa tttagtagat tgaatttttc tagtgatccc taattttta ggggcagtgg 1080

tggttgagtt cacagcatgg aatcagatgg tgtgtgtttg aatgttattt ctatgatttg 1140

caagctgggt aaatttggtc aagaccttaa gttctcttca tctgtaatgt ggggataata 1200

atagttctta ctcatagggc taccctgagg actaagtaaa ttaatacagc atatcctcta 1260

aaacaatgta ttgcatattg taaaccttta ataaatgtta acaattgt 1308

<210> 22

<211> 1272

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (60)...(881)

<400> 22

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atg agg ggc tct cag gag gtg ctg ctg atg tgg ctt ctg gtg ttg gca 107

Met Arg Gly Ser Gln Glu Val Leu Leu Met Trp Leu Leu Val Leu Ala

1 5 10 15

gtg ggc ggc aca gag cac gcc tac cgg ccc ggc cgt agg gtg tgt gct 155
Val Gly Gly Thr Glu His Ala Tyr Arg Pro Gly Arg Arg Val Cys Ala
20 25 30
gtc cgg gct cac ggg gac cct gtc tcc gag tcg ttc gtg cag cgt gtg 203
Val Arg Ala His Gly Asp Pro Val Ser Glu Ser Phe Val Gln Arg Val
35 40 45
tac cag ccc ttc ctc acc acc tgc gac ggg cac cgg gcc tgc agc acc 251
Tyr Gln Pro Phe Leu Thr Thr Cys Asp Gly His Arg Ala Cys Ser Thr
50 55 60
tac cga acc atc tat agg acc gcc tac cgc cgc agc cct ggg ctg gcc 299
Tyr Arg Thr Ile Tyr Arg Thr Ala Tyr Arg Arg Ser Pro Gly Leu Ala
65 70 75 80
cct gcc agg cct cgc tac gcg tgc tgc ccc ggc tgg aag agg acc agc 347
Pro Ala Arg Pro Arg Tyr Ala Cys Cys Pro Gly Trp Lys Arg Thr Ser
85 90 95
ggg ctt cct ggg gcc tgt gga gca gca ata tgc cag ccg cca tgc cgg 395
Gly Leu Pro Gly Ala Cys Gly Ala Ala Ile Cys Gln Pro Pro Cys Arg
100 105 110
aac gga ggg agc tgt gtc cag cct ggc cgc tgc cgc tgc cct gca gga 443
Asn Gly Gly Ser Cys Val Gln Pro Gly Arg Cys Arg Cys Pro Ala Gly
115 120 125
tgg cgg ggt gac act tgc cag tca gat gtg gat gaa tgc agt gct agg 491
Trp Arg Gly Asp Thr Cys Gln Ser Asp Val Asp Glu Cys Ser Ala Arg
130 135 140
agg ggc ggc tgt ccc cag cgc tgc gtc aac acc gcc ggc agt tac tgg 539

Arg Gly Gly Cys Pro Gln Arg Cys Val Asn Thr Ala Gly Ser Tyr Trp

145 150 155 160

tgc cag tgt tgg gag ggg cac agc ctg tct gca gac ggt aca ctc tgt 587

Cys Gln Cys Trp Glu Gly His Ser Leu Ser Ala Asp Gly Thr Leu Cys

165 170 175

gtg ccc aag gga ggg ccc ccc agg gtg gcc ccc aac ccg aca gga gtg 635

Val Pro Lys Gly Gly Pro Pro Arg Val Ala Pro Asn Pro Thr Gly Val

180 185 190

gac agt gca atg aag gaa gaa gtg cag agg ctg cag tcc agg gtg gac 683

Asp Ser Ala Met Lys Glu Glu Val Gln Arg Leu Gln Ser Arg Val Asp

195 200 205

ctg ctg gag gag aag ctg cag ctg gtg ctg gcc cca ctg cac agc ctg 731

Leu Leu Glu Glu Lys Leu Gln Leu Val Leu Ala Pro Leu His Ser Leu

210 215 220

gcc tcg cag gca ctg gag cat ggg ctc ccg gac ccc ggc agc ctc ctg 779

Ala Ser Gln Ala Leu Glu His Gly Leu Pro Asp Pro Gly Ser Leu Leu

225 230 235 240

gtg cac tcc ttc cag cag ctc ggc cgc atc gac tcc ctg agc gag cag 827

Val His Ser Phe Gln Gln Leu Gly Arg Ile Asp Ser Leu Ser Glu Gln

245 250 255

att tcc ttc ctg gag gag cag ctg ggg tcc tgc tcc tgc aag aaa gac 875

Ile Ser Phe Leu Glu Glu Gln Leu Gly Ser Cys Ser Cys Lys Lys Asp

260 265 270

tcg tgactgccca gcgccccagg ctggactgag cccctcacgc cgccctgcag cc 930

Ser

cccatgcccc tgcccaacat gctgggggtc cagaagccac ctcggggtga ctgagcggaa 990

ggccaggcag ggccttcctc ctcttcctcc tccccttcct cgggaggctc cccagaccct 1050

ggcatgggat gggctgggat cttctctgtg aatccacccc tggctacccc caccctggct 1110

accccaacgg catcccaagg ccaggtgggc cctcagctga gggaaggtac gagctccctg 1170

ctggagcctg ggacccatgg cacaggccag gcagcccgga ggctgggtgg ggcctcagtg 1230

ggggctgctg cctgaccccc agcacaataa aaatgaaacg tg 1272

<210> 23

<211> 2083

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (188)...(1036)

<400> 23

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ccgagccgcg gctgcctccc tcgctcactc cctcgcgcac tcgcccgccc cctccctccc 120

tcccctccct tccccggccc cggctctggc cccggcccat tcgctgttgg gtcttctgct 180

agggagg atg tcg ggt tcg tcg ctg ccc agc gcc ctg gcc ctc tcg ctg 229

Met Ser Gly Ser Ser Leu Pro Ser Ala Leu Ala Leu Ser Leu

1 5 10

ttg ctg gtc tct ggc tcc ctc ctc cca ggg cca ggc gcc gct cag aac 277

Leu Leu Val Ser Gly Ser Leu Leu Pro Gly Pro Gly Ala Ala Gln Asn

15 20 25 30

gag cca agg att gtc acc agt gaa gag gtc att att cga gac agc cct 325

Glu Pro Arg Ile Val Thr Ser Glu Glu Val Ile Ile Arg Asp Ser Pro

35 40 45

gtt ctc cct gtc acc ctg cag tgt aac ctc acc tcc agc tct cac acc 373

Val Leu Pro Val Thr Leu Gln Cys Asn Leu Thr Ser Ser Ser His Thr

50 55 60

ctt aca tac agc tac tgg aca aag aat ggg gtg gaa ctg agt gcc act 421

Leu Thr Tyr Ser Tyr Trp Thr Lys Asn Gly Val Glu Leu Ser Ala Thr

65 70 75

cgt aag aat gcc agc aac atg gag tac agg atc aat aag ccg aga gct 469

Arg Lys Asn Ala Ser Asn Met Glu Tyr Arg Ile Asn Lys Pro Arg Ala

80 85 90

gag gat tca ggc gaa tac cac tgc gta tat cac ttt gtc agc gct cct 517

Glu Asp Ser Gly Glu Tyr His Cys Val Tyr His Phe Val Ser Ala Pro

95 100 105 110

aaa gca aac gcc acc att gaa gtg aaa gcc gct cct gac atc act ggc 565

Lys Ala Asn Ala Thr Ile Glu Val Lys Ala Ala Pro Asp Ile Thr Gly

115 120 125

cat aaa cgg agt gag aac aag aat gaa ggg cag gat gcc act atg tat 613

His Lys Arg Ser Glu Asn Lys Asn Glu Gly Gln Asp Ala Thr Met Tyr

130 135 140

tgc aag tca gtt ggc tac ccc cac cca gac tgg ata tgg cgc aag aag 661

Cys Lys Ser Val Gly Tyr Pro His Pro Asp Trp Ile Trp Arg Lys Lys

145 150 155

gag aac ggg atg ccc atg gac att gtc aat acc tct ggc cgc ttc ttc 709

Glu Asn Gly Met Pro Met Asp Ile Val Asn Thr Ser Gly Arg Phe Phe

160 165 170

atc atc aac aag gaa aat tac act gag ttg aac att gtg aac ctg cag 757

Ile Ile Asn Lys Glu Asn Tyr Thr Glu Leu Asn Ile Val Asn Leu Gln

175 180 185 190

atc acg gaa gac cct ggc gag tat gaa tgt aat gcc acc aac gcc att 805

Ile Thr Glu Asp Pro Gly Glu Tyr Glu Cys Asn Ala Thr Asn Ala Ile

195 200 205

ggc tcc gcc tct gtt gtc act gtc ctc agg gtg cgg agc cac ctg gcc 853

Gly Ser Ala Ser Val Val Thr Val Leu Arg Val Arg Ser His Leu Ala

210 215 220

cca ctc tgg cct ttc ttg gga att ctg gct gaa att atc atc ctt gtg 901

Pro Leu Trp Pro Phe Leu Gly Ile Leu Ala Glu Ile Ile Ile Leu Val

225 230 235

gtg atc att gtt gtg tat gag aag agg aag agg cca gat gag gtt cct 949

Val Ile Ile Val Val Tyr Glu Lys Arg Lys Arg Pro Asp Glu Val Pro

240 245 250

gac gat gat gaa cca gct gga cca atg aaa acc aac tct acc aac aat 997

Asp Asp Asp Glu Pro Ala Gly Pro Met Lys Thr Asn Ser Thr Asn Asn

255 260 265 270

cac aaa gat aaa aac ttg cgc cag aga aac aca aat taagtac 1040

His Lys Asp Lys Asn Leu Arg Gln Arg Asn Thr Asn

275 280

tgcttacaat atctttaggt tcctgaaact ggtggcaaca tgacctgcta aaattttctg 1100

cttggacctc tttggttctc tcccctttca agtgagcaac accacaatga ctgtctaaag 1160

catgccttat ttagcctctc ctgtaagggt gatctagcca ggtacatttt aaacaatgct 1220

tcagtgtaga aggtgtaaac tattttgggc ttgatgtgct gtgaatgttg cttttttttt 1280

tcctttgtta aaatatttaa atagaagtga aaaggtcctc tgaggatcag atcatgcatg 1340

cgccattttt tacttaatgc agctgttaaa ttggcaaagc tctaaaatgc actgctgcca 1400

tctagtgata cacttttgta aagtacagca aaacctacag atatatacag tatataaata 1460

tatatatata tatatttata tttttggggg tgggagaaat ccaaaataaa gtaaatgctt 1520

gtttcatttt taagctgctg atattcattc cttattgtat gttgtcagat gaggaaattg 1580

tgcagttctg gtacataaag atgagtaata taaactgaaa tctataattt taagggctta 1640

acctgtgact ttaataagct ggaacagtcc actgaatggg tataatgaat tgcagtatat 1700

acgtatgatt gctttttaag tgattatctt ttcttctgtt aagtcatgta aattcataaa 1760

tccttttgca ctgatgtgtt gaaccttatt cttgtacatt cattcaatca aggcaaactt 1820

ttataatttt tcttttgttt ccaatgacct tgaaatgtta tagcatggta atattctatg 1880

caactatagt tatacttttt ggtttgacac tgtatttttt cacattgatt tactggttga 1940

tgatagattt tataacctaa cggttctcat gcggtgcgta attgtagatg catgtacttg 2000

tgtgttttgt gtaattattg aagtgcaatg atgtataaaa aagtggattc acctgttttt 2060

aaaaataaaa cattgataaa agg 2083

<210> 24

<211> 1260

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (147)...(863)

<400> 24

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gggacgggga gcccccgggg gccccgccac tgccgccgtc cgccgtcacc tacccggact 120

ggatcggcca gagttactcc gaggtg atg agc ctc aac gag cac tcc atg 170

Met Ser Leu Asn Glu His Ser Met

1 5

cag gcg ctg tcc tgg cgc aag ctc tac ttg agc cgc gcc aag ctt aaa 218

Gln Ala Leu Ser Trp Arg Lys Leu Tyr Leu Ser Arg Ala Lys Leu Lys

10 15 20

gcc tcc agc cgg acc tcg gct ctg ctc tcc ggc ttc gcc atg gtg gca 266

Ala Ser Ser Arg Thr Ser Ala Leu Leu Ser Gly Phe Ala Met Val Ala

25 30 35 40

atg gtg gag gtg cag ctg gac gct gac cac gac tac cca ccg ggg ctg 314

Met Val Glu Val Gln Leu Asp Ala Asp His Asp Tyr Pro Pro Gly Leu

45 50 55

ctc atc gcc ttc agt gcc tgc acc aca gtg ctg gtg gct gtg cac ctg 362

Leu Ile Ala Phe Ser Ala Cys Thr Thr Val Leu Val Ala Val His Leu

60 65 70

ttt gcg ctc atg atc agc acc tgc atc ctg ccc aac atc gag gcg gtg 410

Phe Ala Leu Met Ile Ser Thr Cys Ile Leu Pro Asn Ile Glu Ala Val

75 80 85

agc aac gtg cac aat ctc aac tcg gtc aag gag tcc ccc cat gag cgc 458

Ser Asn Val His Asn Leu Asn Ser Val Lys Glu Ser Pro His Glu Arg

90 95 100

atg cac cgc cac atc gag ctg gcc tgg gcc ttc tcc acc gtc atc ggc 506

Met His Arg His Ile Glu Leu Ala Trp Ala Phe Ser Thr Val Ile Gly

105 110 115 120

acg ctg ctc ttc cta gct gag gtg gtg ctg ctc tgc tgg gtc aag ttc 554

Thr Leu Leu Phe Leu Ala Glu Val Val Leu Leu Cys Trp Val Lys Phe

125 130 135

ttg ccc ctc aag aag cag cca ggc cag cca agg ccc acc agc aag ccc 602

Leu Pro Leu Lys Lys Gln Pro Gly Gln Pro Arg Pro Thr Ser Lys Pro

140 145 150

ccc gcc agt ggc gca gca gcc aac gtc agc acc agc ggc atc acc ccg 650

Pro Ala Ser Gly Ala Ala Ala Asn Val Ser Thr Ser Gly Ile Thr Pro

155 160 165

ggc cag gca gct gcc atc gcc tcg acc acc atc atg gtg ccc ttc ggc 698

Gly Gln Ala Ala Ala Ile Ala Ser Thr Thr Ile Met Val Pro Phe Gly

170 175 180

ctg atc ttt atc gtc ttc gcc gtc cac ttc tac cgc tca ctg gtt agc 746

Leu Ile Phe Ile Val Phe Ala Val His Phe Tyr Arg Ser Leu Val Ser

185 190 195 200

cat aag acc gac cga cag ttc cag gag ctc aac gag ctg gcg gag ttt 794

His Lys Thr Asp Arg Gln Phe Gln Glu Leu Asn Glu Leu Ala Glu Phe

205 210 215

gcc cgc tta cag gac cag ctg gac cac aga ggg gac cac ccc ctg acg 842

Ala Arg Leu Gln Asp Gln Leu Asp His Arg Gly Asp His Pro Leu Thr

220 225 230

ccc ggc agc cac tat gcc taggcccatg tggtctgggc ccttccagtg 890

Pro Gly Ser His Tyr Ala

235

ctttggcctt acgcccttcc ccttgacctt gtcctgcccc agcctcacgg acagcctgcg 950

cagggggctg ggcttcagca aggggcagag cgtggaggga agaggatttt tataagagaa 1010

atttctgcac tttgaaactg tcctctaaga gaataagcat ttcctgttct tccagctcca 1070

ggtccacctc ctgttgggag gcggtggggg gccaaagtgg ggccacacac tcgctgtgtc 1130

ccctctcctc ccctgtgcca gtgccacctg ggtgcctcct cctgtcctgt ccgtctcaac 1190

ctccctcccg tccagcattg agtgtgtaca tgtgtgtgtg acacataaat atactcataa 1250

ggacacctcc 1260

<210> 25

<211> 1720

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (282)...(1400)

<400> 25

agcaaagagc agtgcccagc ccagctcaga gggcaaatgg gacagatccc agaggccctg 60

aggaggtctc tgctgctgat gaagctgtga ccaaacgcac ccaacccttg gcagccatct 120

gtccctgcag ccatagccca cattcccatg acctccctct gcttgttttg ggaccatgtc 180

tgtacagcct ctaggcccca gccccggagg tgaatgccat gccatgattc tggtgtgctc 240

catggcatcc ccagcctagc tcccaatccc actttggcac g atg tta gcc aac 293

Met Leu Ala Asn

1

agc tcc tca acc aac agt tct gtt ctc ccg tgt cct gac tac cga cct 341

Ser Ser Ser Thr Asn Ser Ser Val Leu Pro Cys Pro Asp Tyr Arg Pro

5 10 15 20

acc cac cgc ctg cac ttg gtg gtc tac agc ttg gtg ctg gct gcc ggg 389

Thr His Arg Leu His Leu Val Val Tyr Ser Leu Val Leu Ala Ala Gly

25 30 35

ctc ccc ctc aac gcg cta gcc ctc tgg gtc ttc ctg cgc gcg ctg cgc 437

Leu Pro Leu Asn Ala Leu Ala Leu Trp Val Phe Leu Arg Ala Leu Arg

40 45 50

gtg cac tcg gtg gtg agc gtg tac atg tgt aac ctg gcg gcc agc gac 485

Val His Ser Val Val Ser Val Tyr Met Cys Asn Leu Ala Ala Ser Asp

55 60 65

ctg ctc ttc acc ctc tcg ctg ccc gtt cgt ctc tcc tac tac gca ctg 533

Leu Leu Phe Thr Leu Ser Leu Pro Val Arg Leu Ser Tyr Tyr Ala Leu

70 75 80

cac cac tgg ccc ttc ccc gac ctc ctg tgc cag acg acg ggc gcc atc 581

His His Trp Pro Phe Pro Asp Leu Leu Cys Gln Thr Thr Gly Ala Ile

85 90 95 100

ttc cag atg aac atg tac ggc agc tgc atc ttc ctg atg ctc atc aac 629

Phe Gln Met Asn Met Tyr Gly Ser Cys Ile Phe Leu Met Leu Ile Asn

105 110 115

gtg gac cgc tac gcc gcc atc gtg cac ccg ctg cga ctg cgc cac ctg 677
Val Asp Arg Tyr Ala Ala Ile Val His Pro Leu Arg Leu Arg His Leu
120 125 130
cgg cgg ccc cgc gtg gcg cgg ctg ctc tgc ctg ggc gtg tgg gcg ctc 725
Arg Arg Pro Arg Val Ala Arg Leu Leu Cys Leu Gly Val Trp Ala Leu
135 140 145
atc ctg gtg ttt gcc gtg ccc gcc gcc cgc gtg cac agg ccc tcg cgt 773
Ile Leu Val Phe Ala Val Pro Ala Ala Arg Val His Arg Pro Ser Arg
150 155 160
tgc cgc tac cgg gac ctc gag gtg cgc cta tgc ttc gag agc ttc agc 821
Cys Arg Tyr Arg Asp Leu Glu Val Arg Leu Cys Phe Glu Ser Phe Ser
165 170 175 180
gac gag ctg tgg aaa ggc agg ctg ctg ccc ctc gtg ctg ctg gcc gag 869
Asp Glu Leu Trp Lys Gly Arg Leu Leu Pro Leu Val Leu Leu Ala Glu
185 190 195
gcg ctg ggc ttc ctg ctg ccc ctg gcg gcg gtg gtc tac tcg tcg ggc 917
Ala Leu Gly Phe Leu Leu Pro Leu Ala Ala Val Val Tyr Ser Ser Gly
200 205 210
cga gtc ttc tgg acg ctg gcg cgc ccc gac gcc acg cag agc cag cgg 965
Arg Val Phe Trp Thr Leu Ala Arg Pro Asp Ala Thr Gln Ser Gln Arg
215 220 225
cgg cgg aag acc gtg cgc ctc ctg ctg gct aac ctc gtc atc ttc ctg 1013
Arg Arg Lys Thr Val Arg Leu Leu Leu Ala Asn Leu Val Ile Phe Leu
230 235 240
ctg tgc ttc gtg ccc tac aac agc acg ctg gcg gtc tac ggg ctg ctg 1061

Leu Cys Phe Val Pro Tyr Asn Ser Thr Leu Ala Val Tyr Gly Leu Leu
245 250 255 260
cgg agc aag ctg gtg gcg gcc agc gtg cct gcc cgc gat cgc gtg cgc 1109
Arg Ser Lys Leu Val Ala Ala Ser Val Pro Ala Arg Asp Arg Val Arg
265 270 275
ggg gtg ctg atg gtg atg gtg ctg ctg gcc ggc gcc aac tgc gtg ctg 1157
Gly Val Leu Met Val Met Val Leu Leu Ala Gly Ala Asn Cys Val Leu
280 285 290
gac ccg ctg gtg tac tac ttt agc gcc gag ggc ttc cgc aac acc ctg 1205
Asp Pro Leu Val Tyr Tyr Phe Ser Ala Glu Gly Phe Arg Asn Thr Leu
295 300 305
cgc ggc ctg ggc act ccg cac cgg gcc agg acc tcg gcc acc aac ggg 1253
Arg Gly Leu Gly Thr Pro His Arg Ala Arg Thr Ser Ala Thr Asn Gly
310 315 320
acg cgg gcg gcg ctc gcg caa tcc gaa agg tcc gcc gtc acc acc gac 1301
Thr Arg Ala Ala Leu Ala Gln Ser Glu Arg Ser Ala Val Thr Thr Asp
325 330 335 340
gcc acc agg ccg gat gcc gcc agt cag ggg ctg ctc cga ccc tcc gac 1349
Ala Thr Arg Pro Asp Ala Ala Ser Gln Gly Leu Leu Arg Pro Ser Asp
345 350 355
tcc cac tct ctg tct tcc ttc aca cag tgt ccc cag gat tcc gcc ctc 1397
Ser His Ser Leu Ser Ser Phe Thr Gln Cys Pro Gln Asp Ser Ala Leu
360 365 370
tga acacacatgc cattgcgctg tccgtgcccg actcccaacg cctctcgttc 1450
tgggaggctt acagggtgta cacacaagaa ggtgggctgg gcacttggac ctttgggtgg 1510

caattccagc ttagcaacgc agaagagtac aaagtgtgga agccagggcc cagggaaggc 1570

agtgctgctg gaaatggctt ctttaaactg tgagcacgca gagcacccct tctccagcgg 1630

tgggaagtga tgcagagagc ccacccgtgc agagggcaga agaggacgaa atgcctttgg 1690

gtgggcaggg cattaaactg ctaaaagctg 1720

<210> 26

<211> 2237

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (25)...(465)

<400> 26

agttcgcacc tccagctcgg gccg atg tgg aag ctt tgg aga gct gaa gag 51

Met Trp Lys Leu Trp Arg Ala Glu Glu

1 5

ggc gcg gcg gcg ctc ggc ggc gcg ctc ttc ctg ctg ctc ttc gcg cta 99

Gly Ala Ala Ala Leu Gly Gly Ala Leu Phe Leu Leu Leu Phe Ala Leu

10 15 20 25

ggg gtc cgc cag ctg ctg aag cag agg cgg ccg atg ggc ttc ccc ccg 147

Gly Val Arg Gln Leu Leu Lys Gln Arg Arg Pro Met Gly Phe Pro Pro

30 35 40

ggg ccg ccg ggg ctg cca ttt atc ggc aac atc tat tcc ctg gca gcc 195

Gly Pro Pro Gly Leu Pro Phe Ile Gly Asn Ile Tyr Ser Leu Ala Ala
45 50 55
tca tcc gag ctt ccc cat gtc tac atg aga aag cag agc cag gtg tac 243
Ser Ser Glu Leu Pro His Val Tyr Met Arg Lys Gln Ser Gln Val Tyr
60 65 70
gga gag gta cag ccc cga cgg gcc ccg ggc agg gag ggc cgc cag gct 291
Gly Glu Val Gln Pro Arg Arg Ala Pro Gly Arg Glu Gly Arg Gln Ala
75 80 85
ggc ccg ggc tgg cca ggg cct tcc tgg ttg gac tta tgg ccg ccc ctg 339
Gly Pro Gly Trp Pro Gly Pro Ser Trp Leu Asp Leu Trp Pro Pro Leu
90 95 100 105
ggc cga cta gtc ggg acc tct ccg tgt gcc ggc tgc cct ttg agg gac 387
Gly Arg Leu Val Gly Thr Ser Pro Cys Ala Gly Cys Pro Leu Arg Asp
110 115 120
acc cgc ttc ccg ggt ctg gaa ggg aga agt cct cga cgc cgt gcc ccc 435
Thr Arg Phe Pro Gly Leu Glu Gly Arg Ser Pro Arg Arg Arg Ala Pro
125 130 135
ttg cag ggg gag ccc cgc ccc tgc cgg tgacccactc cgggccga 480
Leu Gln Gly Glu Pro Arg Pro Cys Arg
140 145
ggctccgagg cgatccagtc ctgattttcc cgctaccgct cgagctcttg ctcctgcgcc 540
tgcgccgttt ggctcgccag ccgcgccgcc acttcaggtc cagggtggac gcatgccctc 600
aggtgcgggc gtcttgcgag tcggcctcgc agctctgtgg aagctgcacg cggcttgtcg 660
gaaaatcaag gcgttctgag ttctagatgg ttaatagcag gttcttcggt gtctgcagtc 720
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ccgggtagag aggtgccccgg ctcccacccc ttcccagccc cagccctgga gacagcagcc    240
cctagactac tgagggacag cgacagc atg aag gct ccg ggt cgg ctc gtg         291
                              Met Lys Ala Pro Gly Arg Leu Val
                              1               5
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Leu Ile Ile Leu Cys Ser Val Val Phe Ser Ala Val Tyr Ile Leu Leu
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tgc tgc tgg gcc ggc ctg ccc ctc tgc ctg gcc acc tgc ctg gac cac       387
Cys Cys Trp Ala Gly Leu Pro Leu Cys Leu Ala Thr Cys Leu Asp His
25                  30                  35                  40
cac ttc ccc aca ggc tcc agg ccc act gtg ccg gga ccc ctg cac ttc       435
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Cys Arg Ser Cys Ala Val Val Ser Ser Ser Gly Gln Met Leu Gly Ser

75 80 85

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Gly Leu Gly Ala Glu Ile Asp Ser Ala Glu Cys Val Phe Arg Met Asn

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Gln Ala Pro Thr Val Gly Phe Glu Ala Asp Val Gly Gln Arg Ser Thr

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Leu Arg Val Val Ser His Thr Ser Val Pro Leu Leu Leu Arg Asn Tyr

125 130 135

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Ser His Tyr Phe Gln Lys Ala Arg Asp Thr Leu Tyr Met Val Trp Gly

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cag ggc agg cac atg gac cgg gtg ctc ggc ggc cgc acc tac cgc acg 771

Gln Gly Arg His Met Asp Arg Val Leu Gly Gly Arg Thr Tyr Arg Thr

155 160 165

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Leu Leu Gln Leu Thr Arg Met Tyr Pro Gly Leu Gln Val Tyr Thr Phe

170 175 180

acg gag cgc atg atg gcc tac tgc gac cag atc ttc cag gac gag acg 867

Thr Glu Arg Met Met Ala Tyr Cys Asp Gln Ile Phe Gln Asp Glu Thr

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Gly Lys Asn Arg Arg Gln Ser Gly Ser Phe Leu Ser Thr Gly Trp Phe

205 210 215

acc atg atc ctc gcg ctg gag ctg tgt gag gag atc gtg gtc tat ggg 963

Thr Met Ile Leu Ala Leu Glu Leu Cys Glu Glu Ile Val Val Tyr Gly

220 225 230

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Met Val Ser Asp Ser Tyr Cys Arg Glu Lys Ser His Pro Ser Val Pro

235 240 245

tac cac tac ttt gag aag ggc cgg cta gat gag tgt cag atg tac ctg 1059

Tyr His Tyr Phe Glu Lys Gly Arg Leu Asp Glu Cys Gln Met Tyr Leu

250 255 260

gca cac gag cag gcg ccc cga agc gcc cac cgc ttc atc act gag aag 1107

Ala His Glu Gln Ala Pro Arg Ser Ala His Arg Phe Ile Thr Glu Lys

265 270 275 280

gcg gtc ttc tcc cgc tgg gcc aag aag agg ccc atc gtg ttc gcc cat 1155

Ala Val Phe Ser Arg Trp Ala Lys Lys Arg Pro Ile Val Phe Ala His

285 290 295

ccg tcc tgg agg act gag tagcttccgt cgtcctgcca gccgccatgc cgttgcg 1210

Pro Ser Trp Arg Thr Glu

300

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tttgggaatt ccaaagtact cagtggagag aggtgtttca ggagccgtag agccagatcg 240
tcatc atg tct gca ttg tgg ctg ctg ctg ggc ctc ctt gcc ctg atg 287
Met Ser Ala Leu Trp Leu Leu Leu Gly Leu Leu Ala Leu Met

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gac ttg tct gaa agc agc aac tgg gga tgc tat gga aac atc caa agc 335

Asp Leu Ser Glu Ser Ser Asn Trp Gly Cys Tyr Gly Asn Ile Gln Ser

15 20 25 30

ctg gac acc cct gga gca tct tgt ggg att gga aga cgt cac ggc ctg 383

Leu Asp Thr Pro Gly Ala Ser Cys Gly Ile Gly Arg Arg His Gly Leu

35 40 45

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Asn Tyr Cys Gly Val Arg Ala Ser Glu Arg Leu Ala Glu Ile Asp Met

50 55 60

cca tac ctc ctg aaa tat caa ccc atg atg caa acc att ggc caa aag 479

Pro Tyr Leu Leu Lys Tyr Gln Pro Met Met Gln Thr Ile Gly Gln Lys

65 70 75

tac tgc atg gat cct gcc gtg atc gct ggt gtc ttg tcc agg aag tct 527

Tyr Cys Met Asp Pro Ala Val Ile Ala Gly Val Leu Ser Arg Lys Ser

80 85 90

ccc ggt gac aaa att ctg gtc aac atg ggc gat agg act agc atg gtg 575

Pro Gly Asp Lys Ile Leu Val Asn Met Gly Asp Arg Thr Ser Met Val

95 100 105 110

cag gac cct ggc tct caa gct ccc aca tcc tgg att agt gag tct cag 623

Gln Asp Pro Gly Ser Gln Ala Pro Thr Ser Trp Ile Ser Glu Ser Gln

115 120 125

gtt tcc cag aca act gaa gtt ctg act act aga atc aaa gaa atc cag 671

Val Ser Gln Thr Thr Glu Val Leu Thr Thr Arg Ile Lys Glu Ile Gln

130 135 140

agg agg ttt cca acc tgg acc cct gac cag tac ctg aga ggt gga ctc 719

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Cys Ala Tyr Ser Gly Gly Ala Gly Tyr Val Arg Ser Ser Gln Asp Leu

160 165 170

agc tgt gac ttc tgc aat gat gtc ctt gca cga gcc aag tac ctc aag 815

Ser Cys Asp Phe Cys Asn Asp Val Leu Ala Arg Ala Lys Tyr Leu Lys

175 180 185 190

aga cat ggc ttc taacatctca gatgaaaccc aagaccatga tcacatatgc agc 870

Arg His Gly Phe

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cctaaaagtc attaaaataa catgaatcac att 963

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Met Lys

1

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Met Lys Ser Gln Ala Thr Met Ile Cys Cys Leu Val Phe Phe Leu Ser

5 10 15

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Thr Glu Cys Ser His Tyr Arg Ser Lys Ile His Leu Lys Ser Tyr Ser

20 25 30

gaa gtg gcc aac cac atc ctc gac aca gca gcc att tca aac tgg gct 378

Glu Val Ala Asn His Ile Leu Asp Thr Ala Ala Ile Ser Asn Trp Ala

35 40 45 50

ttc att ccc aac aaa aat gcc agc tcg gat ttg ttg cag tca gtg aat 426

Phe Ile Pro Asn Lys Asn Ala Ser Ser Asp Leu Leu Gln Ser Val Asn

55 60 65

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Leu Phe Ala Arg Gln Leu His Ile His Asn Asn Ser Glu Asn Ile Val

70 75 80

aat gaa ctc ttc att cag aca aaa ggg ttt cac atc aac cat aat acc 522

Asn Glu Leu Phe Ile Gln Thr Lys Gly Phe His Ile Asn His Asn Thr

85 90 95

tca gag aaa agc ctc aat ttc tcc atg agc atg aac aat acc aca gaa 570

Ser Glu Lys Ser Leu Asn Phe Ser Met Ser Met Asn Asn Thr Thr Glu
100 105 110

gat atc tta gga atg gta cag att ccc agg caa gag cta agg aag ctg 618
Asp Ile Leu Gly Met Val Gln Ile Pro Arg Gln Glu Leu Arg Lys Leu
115 120 125 130

tgg cca aat gca tcc caa gcc att agc ata gct ttc cca acc ttg ggg 666
Trp Pro Asn Ala Ser Gln Ala Ile Ser Ile Ala Phe Pro Thr Leu Gly
135 140 145

gct atc ctg aga gaa gcc cac ttg caa aat gtg agt ctt ccc aga cag 714
Ala Ile Leu Arg Glu Ala His Leu Gln Asn Val Ser Leu Pro Arg Gln
150 155 160

gta aat ggt ctg gtg cta tca gtg gtt tta cca gaa agg ttg caa gaa 762
Val Asn Gly Leu Val Leu Ser Val Val Leu Pro Glu Arg Leu Gln Glu
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atc ata ctc acc ttc gaa aag atc aat aaa acc cgc aat gcc aga gcc 810
Ile Ile Leu Thr Phe Glu Lys Ile Asn Lys Thr Arg Asn Ala Arg Ala
180 185 190

cag tgt gtt ggc tgg cac tcc aag aaa agg aga tgg gat gag aaa gcg 858
Gln Cys Val Gly Trp His Ser Lys Lys Arg Arg Trp Asp Glu Lys Ala
195 200 205 210

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Cys Gln Met Met Leu Asp Ile Arg Asn Glu Val Lys Cys Arg Cys Asn
215 220 225

tac acc agt gtg gtg atg tct ttt tcc att ctc atg tcc tcc aaa tcg 954
Tyr Thr Ser Val Val Met Ser Phe Ser Ile Leu Met Ser Ser Lys Ser

230 235 240

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Met Thr Asp Lys Val Leu Asp Tyr Ile Thr Cys Ile Gly Leu Ser Val

245 250 255

tca atc cta agc ttg gtt ctt tgc ctg atc att gaa gcc aca gtg tgg 1050

Ser Ile Leu Ser Leu Val Leu Cys Leu Ile Ile Glu Ala Thr Val Trp

260 265 270

tcc cgg gtg gtt gtg acg gag ata tca tac atg cgt cac gtg tgc atc 1098

Ser Arg Val Val Val Thr Glu Ile Ser Tyr Met Arg His Val Cys Ile

275 280 285 290

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Val Asn Ile Ala Val Ser Leu Leu Thr Ala Asn Val Trp Phe Ile Ile

295 300 305

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Gly Ser His Phe Asn Ile Lys Ala Gln Asp Tyr Asn Met Cys Val Ala

310 315 320

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Val Thr Phe Phe Ser His Phe Phe Tyr Leu Ser Leu Phe Phe Trp Met

325 330 335

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Leu Phe Lys Ala Leu Leu Ile Ile Tyr Gly Ile Leu Val Ile Phe Arg

340 345 350

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Arg Met Met Lys Ser Arg Met Met Val Ile Gly Phe Ala Ile Gly Tyr

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Gly Cys Pro Leu Ile Ile Ala Val Thr Thr Val Ala Ile Thr Glu Pro
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gag aac ggc tac atg aga cct gag gcc tgt tgg ctt aac tgg gac aat 1434
Glu Asn Gly Tyr Met Arg Pro Glu Ala Cys Trp Leu Asn Trp Asp Asn
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Thr Lys Ala Leu Leu Ala Phe Ala Ile Pro Ala Phe Val Ile Val Ala
405 410 415

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Val Asn Leu Ile Val Val Leu Val Val Ala Val Asn Thr Gln Arg Pro
420 425 430

tct att ggc agt tcc aag tct cag gat gtg gtc ata att atg agg atc 1578
Ser Ile Gly Ser Ser Lys Ser Gln Asp Val Val Ile Ile Met Arg Ile
435 440 445 450

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Ser Lys Asn Val Ala Ile Leu Thr Pro Leu Leu Gly Leu Thr Trp Gly
455 460 465

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Phe Gly Ile Ala Thr Leu Ile Glu Gly Thr Ser Leu Thr Phe His Ile
470 475 480

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Ile Phe Ala Leu Leu Asn Ala Phe Gln Gly Phe Phe Ile Leu Leu Phe
485 490 495

gga acc att atg gat cac aag ata aga gat gct ttg agg atg agg atg 1770

Gly Thr Ile Met Asp His Lys Ile Arg Asp Ala Leu Arg Met Arg Met

500 505 510

tct tca ctg aag ggg aaa tcg agg gca gct gag aat gca tca cta ggc 1818

Ser Ser Leu Lys Gly Lys Ser Arg Ala Ala Glu Asn Ala Ser Leu Gly

515 520 525 530

cca acc aat gga tct aaa tta atg aat cgt caa gga tgaaatgctg ccccat 1870

Pro Thr Asn Gly Ser Lys Leu Met Asn Arg Gln Gly

535 540

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cagcccgaag cagccagacc agcccctgag cctcccgggt gctggcagct gtc atg      176
                                                           Met
                                                            1
ggg cta ccc tgg ggg cag cct cac cta ggg ctg cag atg ctc ctc ctg     224
Gly Leu Pro Trp Gly Gln Pro His Leu Gly Leu Gln Met Leu Leu Leu
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gcg ttg aac tgt ctc cgg ccc agc ctg agc ctg gag ctg gtg ccc tac     272
Ala Leu Asn Cys Leu Arg Pro Ser Leu Ser Leu Glu Leu Val Pro Tyr
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aca cca cag ata aca gct tgg gac ctg gaa ggg aag gtc aca gcc acc     320
Thr Pro Gln Ile Thr Ala Trp Asp Leu Glu Gly Lys Val Thr Ala Thr
    35                  40                  45
acc ttc tcc ctg gag cag ccg cgc tgt gtc ttc gat ggg ctt gcc agc     368
Thr Phe Ser Leu Glu Gln Pro Arg Cys Val Phe Asp Gly Leu Ala Ser
50                  55                  60                  65
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Ala Ser Asp Thr Val Trp Leu Val Val Ala Phe Ser Asn Ala Ser Arg
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ggc ttc cag aac ccg gag aca ctg gct gac att ccg gcc tcc cca cag 464
Gly Phe Gln Asn Pro Glu Thr Leu Ala Asp Ile Pro Ala Ser Pro Gln
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Leu Leu Thr Asp Gly His Tyr Met Thr Leu Pro Leu Ser Pro Asp Gln
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Leu Pro Cys Gly Asp Pro Met Ala Gly Ser Gly Gly Ala Pro Val Leu
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Arg Val Gly His Asp His Gly Cys His Gln Gln Pro Phe Cys Asn Ala
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Pro Leu Pro Gly Pro Gly Pro Tyr Arg Val Lys Phe Leu Leu Met Asp
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Thr Arg Gly Ser Pro Arg Ala Glu Thr Lys Trp Ser Asp Pro Ile Thr
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ctc cac caa ggg aag acc ccc gga tcc atc gac acc tgg cca ggg cgg 752
Leu His Gln Gly Lys Thr Pro Gly Ser Ile Asp Thr Trp Pro Gly Arg
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Arg Ser Gly Ser Met Ile Val Ile Thr Ser Ile Leu Ser Ser Leu Ala
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ggc ctc cta ctc ttg gcc ttc ttg gca gcc tct acc atg cgc ttc tcc 848
Gly Leu Leu Leu Leu Ala Phe Leu Ala Ala Ser Thr Met Arg Phe Ser
210 215 220 225
agc ctg tgg tgg ccg gag gag gcc ccg gag cag ctg cgg atc ggc tcc 896
Ser Leu Trp Trp Pro Glu Glu Ala Pro Glu Gln Leu Arg Ile Gly Ser
230 235 240
ttc atg ggc aag cgc tac atg acc cac cac atc cca ccc agc gag gcc 944
Phe Met Gly Lys Arg Tyr Met Thr His His Ile Pro Pro Ser Glu Ala
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Ala Thr Leu Pro Val Gly Cys Lys Pro Gly Leu Asp Pro Leu Pro Ser
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275
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